

**DESCRIPTION****METHOD FOR TREATING VASCULAR HYPERPERMEABLE DISEASE****TECHNICAL FIELD**

The present invention relates to a method for treating a  
5 vascular hyperpermeable disease (except macular edema).

**BACKGROUND ART**

Vascular adhesion protein-1 (hereinafter to be  
abbreviated as VAP-1) is amine oxidase (semicarbazide  
sensitive amine oxidase, SSAO) which is abundant in human  
10 plasma, and shows remarkably increased expression in  
vascular endothelium and vascular smooth muscle of the  
inflammatory region. While the physiological role of VAP-1  
has not been clarified until recently, VAP-1 gene was cloned  
in 1998, and VAP-1 has been reported to be a membrane  
15 protein that regulates rolling and migration of lymphocyte  
and NK cell as an adhesion molecule under regulation of  
expression by inflammatory cytokine. Although the amine to  
be a substrate is unknown, it is considered to be  
methylamine generated in any part of living organisms. It is  
20 also known that hydrogen peroxide and aldehydes produced by  
the amine oxidase activity in a molecule are important  
factors of adhesion activity.

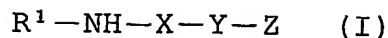
However, the correlation between the VAP-1 enzyme  
activity in plasma and vascular permeability has not been  
25 heretofore known.

**DISCLOSURE OF INVENTION**

The present inventors have found that VAP-1 enzyme  
activity in plasma and vascular permeability are correlated,  
and therefore, a VAP-1 inhibitor is useful for the  
30 prophylaxis or treatment of a vascular hyperpermeable  
disease (except macular edema) and completed the present  
invention. Thus, the present invention provides the  
following.

- (1) A method for treating a vascular hyperpermeable disease (except macular edema), which method comprises administering to a subject in need thereof a vascular adhesion protein-1 (VAP-1) inhibitor in an amount sufficient to treat said  
5 subject for said disease.
- (2) The method of (1), wherein said disease is a disease in mucous membrane.
- (3) The method of (2), wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or  
10 respiratory tract.
- (4) The method of (1), wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy,  
15 neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis,  
20 exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic operation, an ocular inflammatory disease caused by a  
25 physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis, angioneurotic edema, laryngeal edema, glottic edema,  
30 subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.
- (5) The method of (1), wherein the VAP-1 inhibitor is a compound of the formula (I) [hereinafter sometimes referred to

as Compound (I)]:



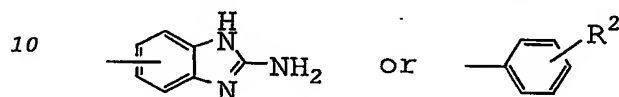
wherein

5  $R^1$  is acyl;

X is a bivalent residue derived from optionally substituted thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:



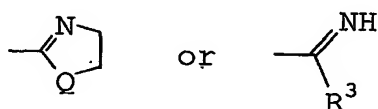
wherein  $R^2$  is a group of the formula: -A-B-D-E

wherein A is a bond, lower alkylene, -NH- or -SO<sub>2</sub>-;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or -CH<sub>2</sub>NH-; and

15 E is optionally protected amino, -N=CH<sub>2</sub>,



wherein

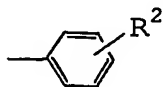
Q is -S- or -NH-; and

20  $R^3$  is hydrogen, lower alkyl, lower alkylthio or -NH- $R^4$  wherein  $R^4$  is hydrogen, -NH<sub>2</sub> or lower alkyl;

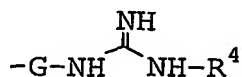
or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

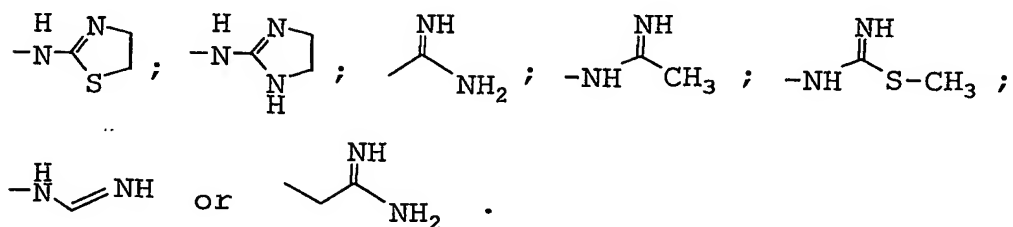
25 (6) The method of (5), wherein, in the formula (I), Z is a group of the formula:



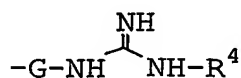
wherein  $R^2$  is a group of the formula:



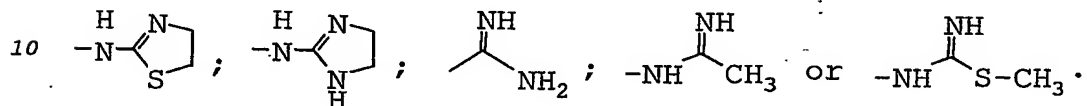
(wherein G is a bond,  $\text{-NHCOCH}_2\text{-}$  or lower alkylene and  $\text{R}^4$  is hydrogen,  $\text{-NH}_2$  or lower alkyl);  $\text{-NH}_2$ ;  $\text{-CH}_2\text{NH}_2$ ;  $\text{-CH}_2\text{ONH}_2$ ;  $\text{-CH}_2\text{ON=CH}_2$ ;



- 5 (7) The method of (6), wherein, in the formula (I),  $\text{R}^2$  is a group of the formula:



(wherein G is a bond,  $\text{-NHCOCH}_2\text{-}$  or lower alkylene and  $\text{R}^4$  is hydrogen or lower alkyl);  $\text{-CH}_2\text{NH}_2$ ;  $\text{-CH}_2\text{ONH}_2$ ;  $\text{-CH}_2\text{ON=CH}_2$ ;



- (8) The method of any of (5) to (7), wherein, in the formula (I),  $\text{R}^1$  is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

(9) The method of (1), wherein the VAP-1 inhibitor is

- 15 N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,  
 N-[4-(2-{4-[(aminooxy)methyl]phenyl)ethyl)-1,3-thiazol-2-yl]acetamide,  
 N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,  
 20 N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,  
 N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or  
 25 N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(10) The method of (1), wherein the VAP-1 inhibitor is  
N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-  
5 thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(11) A pharmaceutical composition for the treatment of a  
vascular hyperpermeable disease (except macular edema), which  
10 comprises, as an active ingredient, a VAP-1 inhibitor.

(12) The composition of (11), wherein said disease is a  
disease in mucous membrane.

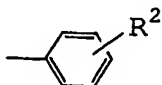
(13) The composition of (12), wherein said mucous membrane is  
a mucous membrane of ocular, cutis, otorhinology or  
15 respiratory tract.

(14) The composition of (11), wherein said disease is aged  
macular degeneration, aged disciform macular degeneration,  
cystoid macular edema, palpebral edema, retinal edema,  
diabetic retinopathy, chorioretinopathy, neovascular  
20 maculopathy, neovascular glaucoma, uveitis, iritis, retinal  
vasculitis, endophthalmitis, panophthalmitis, metastatic  
ophthalmia, choroiditis, retinal pigment epithelitis,  
conjunctivitis, cyclitis, scleritis, episcleritis, optic  
neuritis, retrobulbar optic neuritis, keratitis,  
25 blepharitis, exudative retinal detachment, corneal ulcer,  
conjunctival ulcer, chronic nummular keratitis, Thygeson  
keratitis, progressive Mooren's ulcer, an ocular  
inflammatory disease caused by bacterial or viral infection,  
and by an ophthalmic operation, an ocular inflammatory  
30 disease caused by a physical injury to the eye, a symptom  
caused by an ocular inflammatory disease including itching,  
flare, edema and ulcer, erythema, erythema exsudativum  
multiforme, erythema nodosum, erythema annulare, scleredema,

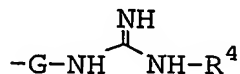
dermatitis, angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

(15) The composition of (11), wherein the VAP-1 inhibitor is  
 5 Compound (I); or a derivative thereof; or a pharmaceutically acceptable salt thereof.

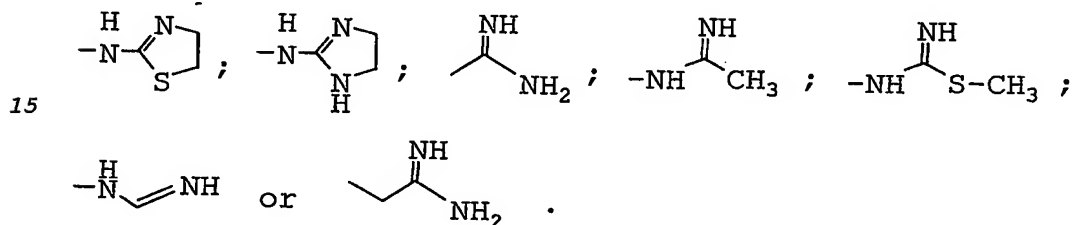
(16) The composition of (15), wherein, in the formula (I), Z is a group of the formula:



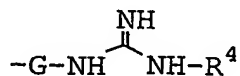
10 wherein R<sup>2</sup> is a group of the formula:



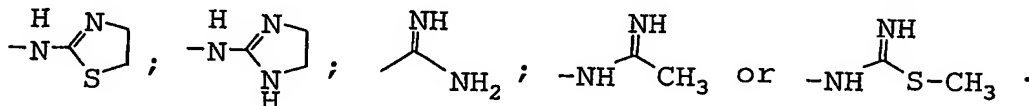
(wherein G is a bond, -NHCOCH<sub>2</sub>- or lower alkylene and R<sup>4</sup> is hydrogen, -NH<sub>2</sub> or lower alkyl); -NH<sub>2</sub>; -CH<sub>2</sub>NH<sub>2</sub>; -CH<sub>2</sub>ONH<sub>2</sub>; -CH<sub>2</sub>ON=CH<sub>2</sub>;



(17) The composition of (16), wherein, in the formula (I), R<sup>2</sup> is a group of the formula:



(wherein G is a bond, -NHCOCH<sub>2</sub>- or lower alkylene and R<sup>4</sup> is  
 20 hydrogen or lower alkyl); -CH<sub>2</sub>NH<sub>2</sub>; -CH<sub>2</sub>ONH<sub>2</sub>; -CH<sub>2</sub>ON=CH<sub>2</sub>;



(18) The composition of any of (15) to (17), wherein, in the formula (I), R<sup>1</sup> is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by

methylsulfonylbenzyl.

(19) The composition of (11), wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

<sup>5</sup> N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

<sup>10</sup> N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

<sup>15</sup> or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(20) The composition of (11), wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

<sup>20</sup> or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(21) A use of a VAP-1 inhibitor for preparing a medicament for the treatment of a vascular hyperpermeable disease (except macular edema).

<sup>25</sup> (22) The use of (21), wherein said disease is a disease in mucous membrane.

(23) The use of (22), wherein said mucous membrane is a mucous membrane of ocular, cutis, otorhinology or respiratory tract.

<sup>30</sup> (24) The use of (21), wherein said disease is aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy,

neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis,

5 retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, an ocular inflammatory disease caused by bacterial or viral infection, and by an ophthalmic

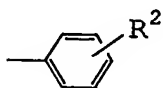
10 operation, an ocular inflammatory disease caused by a physical injury to the eye, a symptom caused by an ocular inflammatory disease including itching, flare, edema and ulcer, erythema, erythema exsudativum multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis,

15 angioneurotic edema, laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis or otitis media.

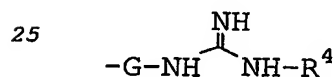
(25) The use of (21), wherein the VAP-1 inhibitor is Compound (I); or a derivative thereof; or a pharmaceutically acceptable

20 salt thereof.

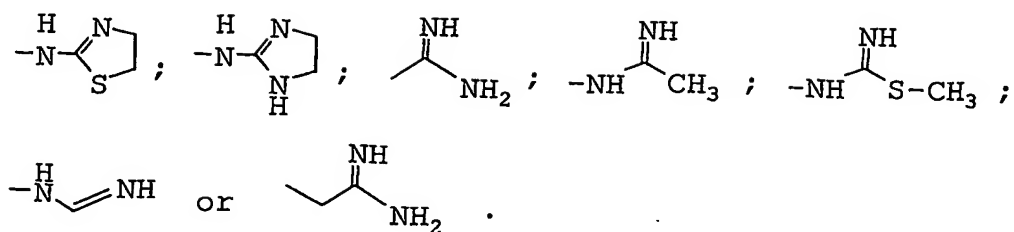
(26) The use of (25), wherein, in the formula (I), Z is a group of the formula:



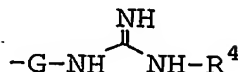
wherein R<sup>2</sup> is a group of the formula:



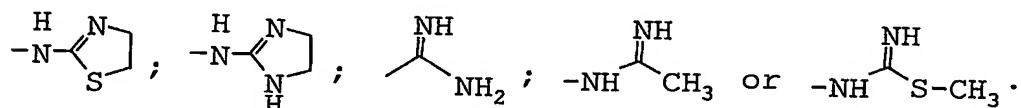
(wherein G is a bond, -NHCOCH<sub>2</sub>- or lower alkylene and R<sup>4</sup> is hydrogen, -NH<sub>2</sub> or lower alkyl); -NH<sub>2</sub>; -CH<sub>2</sub>NH<sub>2</sub>; -CH<sub>2</sub>ONH<sub>2</sub>; -CH<sub>2</sub>ON=CH<sub>2</sub>;



(27) The use of (26), wherein, in the formula (I), R<sup>2</sup> is a group of the formula:



5 (wherein G is a bond, -NHCOCH<sub>2</sub>- or lower alkylene and R<sup>4</sup> is hydrogen or lower alkyl); -CH<sub>2</sub>NH<sub>2</sub>; -CH<sub>2</sub>ONH<sub>2</sub>; -CH<sub>2</sub>ON=CH<sub>2</sub>;



(28) The use of any of (25) to (27), wherein, in the formula (I), R<sup>1</sup> is alkylcarbonyl and X is a bivalent residue derived from thiazole optionally substituted by methylsulfonylbenzyl.

(29) The use of (21), wherein the VAP-1 inhibitor is N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide,

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide,

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide,

N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide, or

N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

(30) The use of (21), wherein the VAP-1 inhibitor is

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide;

or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

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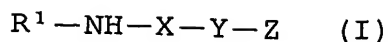
#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated on the discovery that VAP-1 enzyme activity in plasma and vascular permeability are correlated, and therefore, an inhibitor of vascular adhesion protein-1 (VAP-1; also referred to as semicarbaside sensitive amine oxidase (SSAO) or copper-containing amine oxidase) is effective in treating or ameliorating a vascular hyperpermeable disease (except macular edema). Accordingly, the present invention provides a method for treating a vascular hyperpermeable disease (except macular edema). The "treating a vascular hyperpermeable disease (except macular edema)" and "treatment of a vascular hyperpermeable disease (except macular edema)" are intended to include the administration of a compound having a VAP-1 inhibitory activity to a subject for purposes, which can include prophylaxis, amelioration, prevention and cure of a vascular hyperpermeable disease (except macular edema). As used herein, by the "subject" is meant a target of the administration of VAP-1 inhibitor in the present invention, which is specifically any animal such as human, mouse, rat, swine, dog, cat, horse, bovine and the like, especially human. The vascular hyperpermeable disease (except macular edema), which is to be treated by the method of the present invention, includes the disease caused/accompanied by increased vascular permeability, for example, diseases in mucous membrane such as ocular, cutis, otorhinology, respiratory tract and the like. Examples thereof include diseases in ocular-mucous membrane, such as aged macular degeneration, aged disciform macular degeneration, cystoid macular edema, palpebral edema, retinal

edema, diabetic retinopathy, chorioretinopathy, neovascular maculopathy, neovascular glaucoma, uveitis, iritis, retinal vasculitis, endophthalmitis, panophthalmitis, metastatic ophthalmia, choroiditis, retinal pigment epithelitis, 5 conjunctivitis, cyclitis, scleritis, episcleritis, optic neuritis, retrobulbar optic neuritis, keratitis, blepharitis, exudative retinal detachment, corneal ulcer, conjunctival ulcer, chronic nummular keratitis, Thygeson keratitis, progressive Mooren's ulcer, ocular inflammatory diseases 10 caused by bacterial or viral infection, and by an ophthalmic operation, ocular inflammatory diseases caused by a physical injury to the eye and symptoms caused by ocular inflammatory diseases including itching, flare, edema and ulcer; mucocutaneous diseases, such as erythema, erythema exsudativum 15 multiforme, erythema nodosum, erythema annulare, scleredema, dermatitis and angioneurotic edema; and diseases in mucous membrane (e.g., otorhinology, respiratory tract etc.), such as laryngeal edema, glottic edema, subglottic laryngitis, bronchitis, rhinitis, pharyngitis, sinusitis, laryngitis and 20 otitis media.

The method comprises the administration of a VAP-1 inhibitor in an amount sufficient to treat a vascular hyperpermeable disease (except macular edema). Any VAP-1 inhibitor can be used in the method of the present invention 25 as long as it is safe and efficacious. Herein, the "VAP-1 inhibitor" will be used to refer to such compounds and is intended to encompass all compounds that inhibit enzyme activity of VAP-1 at any and all points in the action mechanism thereof.

30 The VAP-1 inhibitor in the present invention includes, for example, a compound represented by the following formula (I) [Compound (I)]:



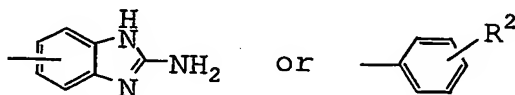
wherein

$R^1$  is acyl;

X is a bivalent residue derived from optionally substituted  
5 thiazole;

Y is a bond, lower alkylene, lower alkenylene or -CONH-; and

Z is a group of the formula:



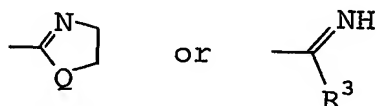
wherein  $R^2$  is a group of the formula: -A-B-D-E

10 wherein A is a bond, lower alkylene, -NH- or -SO<sub>2</sub>-;

B is a bond, lower alkylene, -CO- or -O-;

D is a bond, lower alkylene, -NH- or -CH<sub>2</sub>NH-; and

E is optionally protected amino, -N=CH<sub>2</sub>,



15 wherein

Q is -S- or -NH-; and

$R^3$  is hydrogen, lower alkyl, lower alkylthio or  
-NH- $R^4$  wherein  $R^4$  is hydrogen, -NH<sub>2</sub> or  
lower alkyl;

20 or a derivative thereof;

or a pharmaceutically acceptable salt thereof.

The definition of each group of Compound (I) is shown  
in the following.

Suitable "halogen" includes fluorine, chlorine, bromine  
25 and iodine.

The term "lower" is used to intend a group having 1 to  
6, preferably 1 to 4, carbon atom(s), unless otherwise  
provided.

Suitable "lower alkyl" includes straight or branched  
30 alkyl having 1 to 6 carbon atom(s), such as methyl, ethyl,

propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is C<sub>1</sub>-C<sub>4</sub> alkyl.

Suitable "lower alkylthio" includes lower alkylthio  
5 containing the above lower alkyl, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, tert-pentylthio and hexylthio.

Suitable "lower alkylene" includes straight or branched  
10 alkylene having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, propylene, ethylidene and propylidene, in which more preferred one is C<sub>1</sub>-C<sub>4</sub> alkylene.

Suitable "lower alkenylene" includes straight or  
15 branched alkenylene having 2 to 6 carbon atom(s), such as -CH=CH-, -CH<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH=CH-CH<sub>2</sub>-CH<sub>2</sub>- and -CH=CH-CH=CH-CH=CH-, in which more preferred one is C<sub>2</sub>-C<sub>4</sub> alkenylene.

20 The above lower alkenylene may be in E or Z form, respectively. Thus, those skilled in the art will recognize that the lower alkenylene includes all E, Z-structures when it has 2 or more double bonds.

Suitable "aryl" includes C<sub>6</sub>-C<sub>10</sub> aryl such as phenyl and  
25 naphthyl, in which more preferred one is phenyl. The "aryl" may be substituted by 1 to 3 substituent(s) and the substitution sites are not particularly limited.

Suitable "aralkyl" includes aralkyl wherein the aryl moiety has 6 to 10 carbon atoms [i.e. the aryl moiety is C<sub>6</sub>-  
30 C<sub>10</sub> aryl of the above "aryl"] and the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C<sub>1</sub>-C<sub>6</sub> alkyl of the above "lower alkyl"], such as benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-phenylpropyl, 4-

phenylbutyl and 5-phenylpentyl.

The "optionally protected amino" means that an amino group may be protected with a suitable protecting group according to a method known *per se*, such as the methods  
5 described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like. The suitable "protecting group" includes tert-butoxycarbonyl (i.e., Boc), an acyl group as mentioned below, substituted or unsubstituted aryl(lower)alkylidene [e.g., benzylidene,  
10 hydroxybenzylidene, etc.], aryl(lower)alkyl such as mono-, di- or triphenyl-(lower)alkyl [e.g., benzyl, phenethyl, benzhydryl, trityl, etc.] and the like.

Suitable "optionally protected amino" includes amino and tert-butoxycarbonylamino (i.e. -NHBoc).

15 Suitable "heterocycle" includes "aromatic heterocycle" and "non-aromatic heterocycle".

Suitable "aromatic heterocycle" includes 5 to 10-membered aromatic heterocycle containing 1 to 3 heteroatom(s) selected from nitrogen, oxygen and sulfur  
20 atoms besides carbon atom(s), and includes, for example, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, pyrimidine, pyrazine and the like.

Suitable "non-aromatic heterocycle" includes 5 to 10-  
25 membered non-aromatic heterocycle containing 1 to 3 heteroatom(s) selected from nitrogen, oxygen and sulfur atoms besides carbon atom(s), and includes, for example, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine,  
30 dioxolan, oxazolidine, thiazolidine, triazolidine and the like.

Suitable "acyl" includes acyl having 1 to 20 carbon atom(s), such as formyl, alkylcarbonyl, arylcarbonyl,

alkoxycarbonyl and aralkyloxycarbonyl.

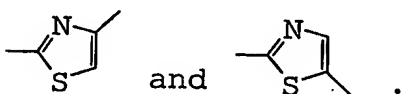
Suitable "alkylcarbonyl" includes alkylcarbonyl wherein the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C<sub>1</sub>-C<sub>6</sub> alkyl of the above "lower alkyl"], such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and heptanoyl, in which more preferred one is C<sub>1</sub>-C<sub>4</sub> alkyl-carbonyl.

Suitable "arylcarbonyl" includes arylcarbonyl wherein the aryl moiety has 6 to 10 carbon atom(s) [i.e. the aryl moiety is C<sub>6</sub>-C<sub>10</sub> aryl of the above "aryl"], such as benzoyl and naphthoyl.

Suitable "alkoxycarbonyl" includes alkoxycarbonyl wherein the alkoxy moiety has 1 to 6 carbon atom(s), such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl and hexyloxycarbonyl, in which more preferred one is alkoxycarbonyl wherein the alkoxy moiety has 1 to 4 carbon atom(s).

Suitable "aralkyloxycarbonyl" includes aralkyloxycarbonyl wherein the aryl moiety has 6 to 10 carbon atom(s) [i.e. the aryl moiety is C<sub>6</sub>-C<sub>10</sub> aryl of the above "aryl"] and the alkyl moiety has 1 to 6 carbon atom(s) [i.e. the alkyl moiety is C<sub>1</sub>-C<sub>6</sub> alkyl of the above "lower alkyl"], such as benzyloxycarbonyl, phenethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl and 5-phenylpentyloxycarbonyl.

Suitable "bivalent residue derived from thiazole" of the "bivalent residue derived from optionally substituted thiazole" includes



The "thiazole" may have 1 to 3 substituent(s) and the substitution sites are not particularly limited.

Suitable "substituent" of the above "optionally substituted thiazole" includes, for example,

5 (1) halogen which is as defined above;

(2) alkoxy carbonyl which is as defined above, such as ethoxy carbonyl;

(3) optionally substituted aryl, which aryl is as defined above and the substitution sites are not  
10 particularly limited, such as phenyl and 4-(methylsulfonyl)phenyl;

(4) a group of the formula:  $-\text{CONR}^a\text{R}^b$  wherein  $\text{R}^a$  is hydrogen, lower alkyl, aryl or aralkyl and  $\text{R}^b$  is hydrogen, lower alkyl, aryl or aralkyl, wherein the lower alkyl, aryl  
15 and aralkyl are as defined above, such as N-methylaminocarbonyl, N-phenylaminocarbonyl, N,N-dimethylaminocarbonyl and N-benzylaminocarbonyl;

(5) a group of the formula:  $-\text{CONH}-(\text{CH}_2)_k\text{-aryl}$  wherein k is an integer of 0 to 6; the aryl is as defined  
20 above, which may have 1 to 5 substituent(s) selected from the group consisting of  $-\text{NO}_2$ ,  $-\text{SO}_2$ -(lower alkyl) wherein the lower alkyl is as defined above,  $-\text{CF}_3$  and  $-\text{O-aryl}$  wherein the aryl is as defined above, and the substitution sites are not particularly limited;

25 (6) a group of the formula:  $-\text{CONH}-(\text{CH}_2)_m\text{-heterocycle}$  wherein m is an integer of 0 to 6; the heterocycle is as defined above, such as pyridine;

(7) a group of the formula:  $-\text{CO-heterocycle}$  wherein the heterocycle is as defined above, such as  
30 pyrrolidine, piperidine, piperazine, thiomorpholine, which may have 1 to 5 substituent(s) selected from the group consisting of  $-\text{CO}-(\text{lower alkyl})$  wherein the lower alkyl is as defined above,  $-\text{CO-O}-(\text{lower alkyl})$  wherein the lower

alkyl is as defined above,  $-\text{SO}_2-(\text{lower alkyl})$  wherein the lower alkyl is as defined above, oxo (i.e.  $=\text{O}$ ) and a group of the formula:  $-\text{CONR}^c\text{R}^d$  wherein  $\text{R}^c$  is hydrogen, lower alkyl, aryl or aralkyl and  $\text{R}^d$  is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(8) a group of the formula:  $-(\text{CH}_2)_n\text{-aryl}$  wherein  $n$  is an integer of 1 to 6; the aryl is as defined above, which may have 1 to 5 substituent(s) selected from the group consisting of  $-\text{S}-(\text{lower alkyl})$  wherein the lower alkyl is as defined above,  $-\text{SO}_2-(\text{lower alkyl})$  wherein the lower alkyl is as defined above,  $-\text{CO}_2-(\text{lower alkyl})$  wherein the lower alkyl is as defined above,  $-\text{NHCO-O}-(\text{lower alkyl})$  wherein the lower alkyl is as defined above and a group of the formula:  $-\text{CONR}^e\text{R}^f$  wherein  $\text{R}^e$  is hydrogen, lower alkyl, aryl or aralkyl and  $\text{R}^f$  is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(9) a group of the formula:  $-(\text{CH}_2)_o\text{-heterocycle}$  wherein  $o$  is an integer of 0 to 6; the heterocycle is as defined above, such as pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, which may have 1 to 5 substituent(s) selected from the group consisting of oxo (i.e.  $=\text{O}$ );  $-\text{CO}-(\text{lower alkyl})$  wherein the lower alkyl is as defined above;  $-\text{CO-O}-(\text{lower alkyl})$  wherein the lower alkyl is as defined above;  $-\text{SO}_2-(\text{lower alkyl})$  wherein the lower alkyl is as defined above;  $-\text{CO}-(\text{heterocycle})$  wherein the heterocycle is as defined above such as pyrrolidine, piperazine and morpholine, which may have 1 to 5 substituent(s) selected from the group consisting of lower alkyl and halogen, wherein the lower alkyl and halogen are

as defined above, and the substitution sites are not particularly limited; and a group of the formula:  $-\text{CONR}^g\text{R}^h$  wherein  $\text{R}^g$  is hydrogen, lower alkyl, aryl or aralkyl and  $\text{R}^h$  is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(10) a group of the formula:  $-(\text{CH}_2)_p-\text{NR}^i\text{R}^j$  wherein  $p$  is an integer of 0 to 6;  $\text{R}^i$  is hydrogen, acyl, lower alkyl, aryl or aralkyl and  $\text{R}^j$  is hydrogen, acyl, lower alkyl, aryl or aralkyl wherein the acyl, lower alkyl, aryl and aralkyl are as defined above, and the lower alkyl may have 1 to 5 substituent(s) selected from the group consisting of a group of the formula:  $-\text{CONR}^k\text{R}^l$  wherein  $\text{R}^k$  is hydrogen, lower alkyl, aryl or aralkyl and  $\text{R}^l$  is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above, and the substitution sites are not particularly limited;

(11) a group of the formula:  $-\text{CON}(\text{H or lower alkyl})-(\text{CHR}^m)_q-\text{T}$  wherein  $q$  is an integer of 0 to 6; the lower alkyl is as defined above;  $\text{R}^m$  is hydrogen, aralkyl which is as defined above, or alkyl which is as defined above, which may be substituted by 1 to 3 substituent(s) selected from the group consisting of  $-\text{OH}$  and  $-\text{CONH}_2$  and the substitution sites are not particularly limited; and  $\text{T}$  is hydrogen; a group of the formula:  $-\text{CONR}^n\text{R}^o$  wherein  $\text{R}^n$  is hydrogen, lower alkyl, aryl or aralkyl and  $\text{R}^o$  is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as defined above;  $-\text{NH}-\text{CO}-\text{R}^p$  wherein  $\text{R}^p$  is lower alkyl which is as defined above or aralkyl which is as defined above;  $-\text{NH}-\text{SO}_2-(\text{lower alkyl})$  wherein the lower alkyl is as defined above;  $-\text{SO}_2-(\text{lower alkyl})$  wherein the lower alkyl is as defined above;  $-\text{heterocycle}$  wherein the heterocycle is as

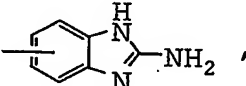
defined above, such as pyridine, pyrrolidine and morpholine, which may have 1 to 3 substituent(s) such as oxo (i.e. =O), and the substitution sites are not particularly limited; or -CO-(heterocycle) wherein the heterocycle is as defined  
5 above, such as piperidine and morpholine; and

(12) a group of the formula:  $-(CH_2)_r-CO-NR^tR^u$  wherein r is an integer of 1 to 6;  $R^t$  is hydrogen, lower alkyl, aryl or aralkyl and  $R^u$  is hydrogen, lower alkyl, aryl or aralkyl wherein the lower alkyl, aryl and aralkyl are as  
10 defined above.

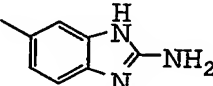
The substitution site on the aryl or heterocycle is any suitable position thereof, but not particularly limited.

Preferable "substituent" of the above "optionally substituted thiazole" is methylsulfonylbenzyl.

15 The substitution sites of  $R^2$  on the phenyl in Compound (I) is not particularly limited.

When Z is a group of the formula: 

the substitution sites on the group are not particularly

limited.  is particularly preferable.

20 Any nitrogen atom in the amino (i.e.  $-NH_2$ ), imino (i.e.  $=NH$  or  $-NH-$ ) or the like contained in Compound (I) may be protected according to the methods, which are known to those skilled in the art, such as the methods described in Protective Groups in Organic Synthesis, published by John  
25 Wiley and Sons (1980), and the like.

When Compound (I) has an asymmetric carbon atom in the structure, those skilled in the art will recognize that Compound (I) includes all stereoisomers.

For example, the Compound (I) and derivatives thereof,  
30 or compounds reported to have inhibited VAP-1 enzyme (SSAO) may include fluoroallylamine derivatives, semicarbazide

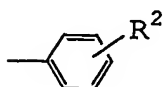
derivatives, hydrazide derivatives, hydrazino derivatives, 1,3,4-oxadiazine derivatives, 2,6-diethoxybenzylamine, 2,6-di(n-propoxy)benzylamine, 2,6-diisopropoxybenzylamine, 2,6-di(n-butoxy)benzylamine, 2,6-bis(methoxymethoxy)benzylamine, 2,6-bis(methoxymethyl)benzylamine, 2,6-diethylbenzylamine, 2,6-di-n-propylbenzylamine, 2,6-bis(2-hydroxyethoxy)benzylamine, and the like.

The above compounds can be exemplified as follows.

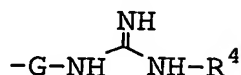
- 1) fluoroallylamine derivatives, semicarbazide derivatives and hydrazide derivatives described in WO 93/23023,
- 2) hydrazino derivatives described in WO 02/02090,
- 3) 1,3,4-oxadiazine derivatives described in WO 02/02541,
- 4) 4-alkyl-5-alkoxycarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine derivatives described in WO 02/38153,
- 5) 2,6-diethoxybenzylamine, 2,6-di(n-propoxy)benzylamine, 2,6-diisopropoxybenzylamine, 2,6-di(n-butoxy)benzylamine, 2,6-bis(methoxymethoxy)benzylamine, 2,6-bis(methoxymethyl)benzylamine, 2,6-diethylbenzylamine, 2,6-di-n-propylbenzylamine and 2,6-bis(2-hydroxyethoxy)benzylamine described in USP 4,888,283.

The compounds exemplified in the present invention as a VAP-1 inhibitor and in WO 93/23023 as an SSAO inhibitor, such as those described in Lyles et al. (Biochem. Pharmacol. 36:2847, 1987) and in USP 4650907, USP 4916151, USP 4943593, USP 4965288, USP 5021456, USP 5059714, USP 4699928, European patent application 295604, European patent application 224924 and European patent application 168013, are also encompassed in the VAP-1 inhibitor.

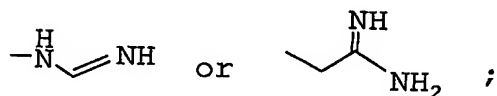
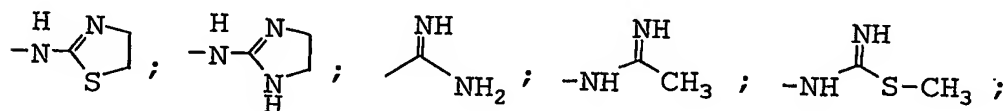
Of the above-mentioned compounds, preferred is Compound (I), more preferably, a compound of the formula (I) wherein Z is a group of the formula:



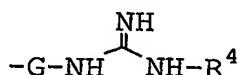
wherein R<sup>2</sup> is a group of the formula:



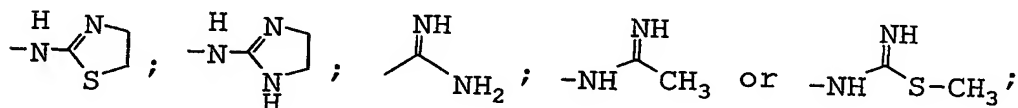
(wherein G is a bond, -NHCOCH<sub>2</sub>- or lower alkylene and R<sup>4</sup> is hydrogen, -NH<sub>2</sub> or lower alkyl); -NH<sub>2</sub>; -CH<sub>2</sub>NH<sub>2</sub>; -CH<sub>2</sub>ONH<sub>2</sub>;  
 5 -CH<sub>2</sub>ON=CH<sub>2</sub>;



still more preferably, a compound wherein R<sup>2</sup> is a group of the formula:



10 (wherein G is a bond, -NHCOCH<sub>2</sub>- or lower alkylene and R<sup>4</sup> is hydrogen or lower alkyl); -CH<sub>2</sub>NH<sub>2</sub>; -CH<sub>2</sub>ONH<sub>2</sub>; -CH<sub>2</sub>ON=CH<sub>2</sub>;



, and yet more preferably, a compound wherein R<sup>1</sup> is alkylcarbonyl and X is a bivalent residue derived from  
 15 thiazole optionally substituted by methylsulfonylbenzyl and derivatives thereof.

Of the above-mentioned Compound (I), preferable specific compounds include

N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-  
 20 thiazol-2-yl}acetamide (hereinafter Compound A; see Production Example 1),

N-[4-(2-{4-[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (hereinafter Compound B; see Production Example 16),

25 N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-

(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (see Production Example 48),  
N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (see  
5 Production Example 50),  
N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (see Production Example 58), and  
N-(4-{2-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (see Production Example 110),  
10 particularly N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide and derivatives thereof.

The term "derivative" is intended to include all compounds derived from the original compound.

15 In the present invention, the VAP-1 inhibitor can be administered as a prodrug to a subject. The term "prodrug" is intended to include all compounds that convert to the VAP-1 inhibitor in the body of administration subject. The prodrug can be any pharmaceutically acceptable prodrug of  
20 VAP-1 inhibitor. Moreover, the VAP-1 inhibitor can be administered to an administration subject as a pharmaceutically acceptable salt.

The pharmaceutically acceptable salt of VAP-1 inhibitor in the present invention is nontoxic and a pharmaceutically  
25 acceptable conventional salt, which is exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-  
30 benzyl-N-methylamine salt and the like).

The VAP-1 inhibitor can be also formulated as a pharmaceutically acceptable acid addition salt. Examples of the pharmaceutically acceptable acid addition salts for use in

the pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, hydriodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, 5 fumaric, benzoic, glycolic, gluconic, succinic and arylsulfonic acids, for example, p-toluenesulfonic acid.

As a pharmaceutically acceptable salt of VAP-1 inhibitor represented by the formula (I), a pharmaceutically acceptable acid addition salt such as (mono-, di- or tri-)hydrochloride 10 and hydriodide, particularly hydrochloride, is preferable.

The above-mentioned VAP-1 inhibitor may be commercially available or can be produced based on a known reference.

Also, Compound (I), particularly Compound A: N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide and Compound B: N-[4-(2-{4- 15 [(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide, can be synthesized according to the Production Method given below.

Those compounds or derivatives thereof that are not 20 commercially available can be prepared using organic synthetic methods known in the art.

The VAP-1 inhibitor or a pharmaceutically acceptable salt thereof can be administered in accordance with the present inventive method by any suitable route. Suitable 25 routes of administration include systemic, such as orally or by injection, topical, periocular (e.g., subTenon's), subconjunctival, intraocular, intravitreal, intracameral, subretinal, suprachoroidal and retrobulbar administrations. The manner in which the VAP-1 inhibitor is administered is 30 dependent, in part, upon whether the treatment of a vascular hyperpermeable disease (except macular edema) is prophylactic or therapeutic.

The VAP-1 inhibitor is preferably administered as soon

as possible after it has been determined that a subject such as a mammal, specifically a human, is at risk for a vascular hyperpermeable disease (except macular edema) (prophylactic treatments) or has begun to develop a vascular

5 hyperpermeable disease (except macular edema) (therapeutic treatments). Treatment will depend, in part, upon the particular VAP-1 inhibitor used, the amount of the VAP-1 inhibitor administered, the route of administration, and the cause and extent, if any, of a vascular hyperpermeable

10 disease (except macular edema) realized.

One skilled in the art will appreciate that suitable methods of administering a VAP-1 inhibitor, which is useful in the present inventive method, are available. Although more than one route can be used to administer a particular

15 VAP-1 inhibitor, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, the described routes of administration are merely exemplary and are in no way limiting.

The dose of the VAP-1 inhibitor administered to the

20 administration subject such as animal including human, particularly a human, in accordance with the present invention should be sufficient to effect the desired response in the subject over a reasonable time frame. One skilled in the art will recognize that dosage will depend

25 upon a variety of factors, including the strength of the particular VAP-1 inhibitor to be employed, the age, species, conditions or disease states, and body weight of the subject, as well as the degree of a vascular hyperpermeable disease (except macular edema). The size of the dose also

30 will be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular VAP-1 inhibitor and the

desired physiological effect. It will be appreciated by one of ordinary skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

5        Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by  
10 small increments until the optimum effect under the circumstances is reached.

Generally, the VAP-1 inhibitor can be administered in the dose of from 0.001  $\mu\text{g/kg/day}$  to about 300  $\text{mg/kg/day}$ , preferably from about 0.01  $\mu\text{g/kg/day}$  to about 10  $\text{mg/kg/day}$ ,  
15 which is given in a single dose or 2 to 4 doses a day or in a sustained manner.

Pharmaceutical compositions for use in the present inventive method preferably comprise a "pharmaceutically acceptable carrier" and an amount of a VAP-1 inhibitor  
20 sufficient to treat a vascular hyperpermeable disease (except macular edema) prophylactically or therapeutically as an active ingredient. The carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity  
25 with the compound, and by the route of administration.

The amount of the VAP-1 inhibitor in the composition may vary depending on the formulation of the composition, and may generally be 0.00001 - 10.0 wt%, preferably 0.0001 - 5 wt%, more preferably 0.001 - 1 wt%.

30        The VAP-1 inhibitor can be administered in various manners to achieve the desired VAP-1 inhibitory effect. The VAP-1 inhibitors can be administered alone or in combination with pharmaceutically acceptable carriers or diluents, the

properties and nature of which are determined by the solubility and chemical properties of the inhibitor selected, the chosen administration route, and standard pharmaceutical practice. The VAP-1 inhibitor may be  
5 administered orally in solid dosage forms, e.g., capsules, tablets, powders, or in liquid forms, e.g., solutions or suspensions. The inhibitor may also be injected parenterally in the form of sterile solutions or suspensions. Solid oral forms may contain conventional excipients, for instance,  
10 lactose, sucrose, magnesium stearate, resins, and like materials. Liquid oral forms may contain various flavoring, coloring, preserving, stabilizing, solubilizing, or suspending agents. Parenteral preparations are sterile aqueous or non-aqueous solutions or suspensions which may  
15 contain certain various preserving, stabilizing, buffering, solubilizing, or suspending agents. If desired, additives, such as saline or glucose, may be added to make the solutions isotonic.

The present inventive method also can involve the co-  
20 administration of other pharmaceutically active compounds. By "co-administration" is meant administration before, concurrently with, e.g., in combination with the VAP-1 inhibitor in the same formulation or in separate formulations, or after administration of a VAP-1 inhibitor  
25 as described above. For example, corticosteroids, prednisone, methylprednisolone, dexamethasone, or triamcinolone acetonide, or noncorticosteroid anti-inflammatory compounds, such as ibuprofen or flubiprofen, can be co-administered. Similarly, vitamins and minerals,  
30 e.g., zinc, anti-oxidants, e.g., carotenoids (such as a xanthophyll carotenoid like zeaxanthin or lutein), and micronutrients can be co-administered.

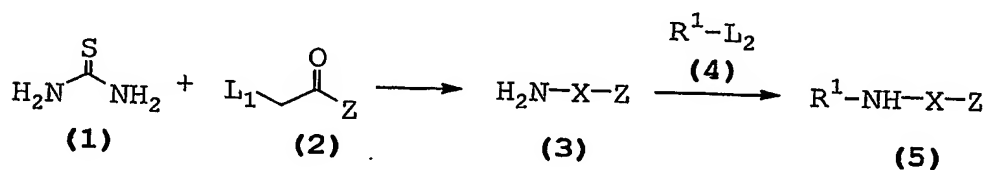
In addition, the present invention provides a use of a

VAP-1 inhibitor for preparing a medicament for the treatment of a vascular hyperpermeable disease (except macular edema).

### Production Method of Compound (I)

Compound (I) is prepared in accordance with, but is not limited to, the following procedures. Those skilled in the art will recognize that the procedures can be modified according to the conventional methods known *per se*.

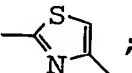
**Procedure A:** Synthesis of Compound (I) wherein Y is a bond



wherein

L<sub>1</sub> is a leaving group such as halogen (e.g., chlorine, bromine, iodine);

Z is as defined above;

X is as defined above, in this case, ;

R<sup>1</sup> is acyl; and

L<sub>2</sub> is a leaving group such as -OH, halogen (e.g., chlorine, bromine, iodine), -O-acyl wherein the acyl is as defined above (e.g., -O-acetyl and the like).

### Formation of Thiazole Moiety X

Compound (1) is reacted with Compound (2) or its salt to give Compound (3).

Suitable salt of Compound (2) may be the same as those exemplified for Compound (I).

Compounds (1) and (2) or its salt may be commercially available or can be prepared in accordance with the methods known *per se* (see Production Example 11).

The reaction is usually carried out in a conventional solvent such as ethanol, acetone, dichloromethane, acetic acid, and other organic solvent which does not adversely affect the reaction, or a mixture thereof.

5 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Compound (3) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, 10 crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

#### Acylation

15 Compound (3) or its salt is reacted with Compound (4) to give Compound (5). Since  $R^1$  is an acyl group, this reaction is an acylation.

The conventional acylation method may be employed in the present invention.

20 Compound (4) may be commercially available or can be prepared in accordance with the methods known *per se*.

The reaction is usually carried out in a conventional solvent such as dichloromethane, chloroform, methanol, and other organic solvent which does not adversely affect the 25 reaction, or a mixture thereof.

The reaction is also preferably carried out in the presence of a conventional base such as 4-dimethylaminopyridine, pyridine etc. A liquid base can be also used as the solvent.

30 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

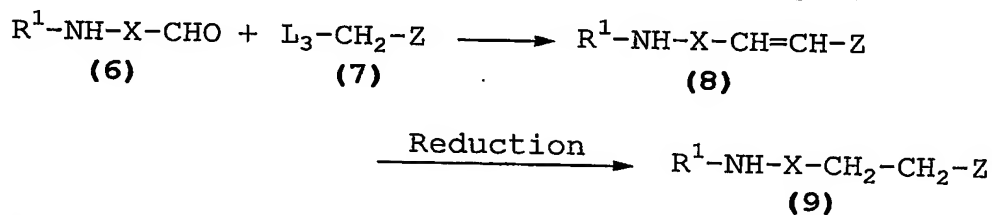
Compound (5) thus obtained can be isolated or purified by known separation or purification means, such as

concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

5 The acylation may be applied to Compound (1) in advance.

The nitrogen atom in Compound (1), (2), (3) or (5) may be protected or deprotected, as necessary, in accordance with methods known *per se* such as the methods described in  
 10 Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

**Procedure B:** Synthesis of Compound (I) wherein Y is lower alkylene such as ethylene (i.e. -CH<sub>2</sub>-CH<sub>2</sub>-) or lower alkenylene  
 15 such as vinylene (i.e. -CH=CH-), for example,



wherein

L<sub>3</sub> is a leaving group such as halogen (e.g., chlorine, bromine, iodine); and

20 R<sup>1</sup>, X and Z are as defined above.

#### Formation of Olefin Compound

Compound (6) or its salt is reacted with Compound (7) or its salt to give an olefin compound (8).

25 Suitable salts of Compounds (6) and (7) may be the same as those exemplified for Compound (I).

Compounds (6) and (7) or salts thereof may be commercially available or can be prepared in accordance with the methods known *per se* (see Production Example 1 and 3).

30 The reaction is usually carried out in a conventional

solvent such as N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, and other organic solvent which does not adversely affect the reaction, or a mixture thereof.

5 The reaction is also usually carried out in the presence of triphenylphosphine and a conventional base such as potassium tert-butoxide, sodium hydride, sodium hydroxide and the like.

The reaction temperature is not critical, and the  
10 reaction can be carried out under cooling to heating.

Compound (8) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer,  
15 chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

#### Reduction

Compound (8) or its salt is reduced in accordance with  
20 a conventional method to give Compound (9).

The conventional reduction includes hydrogenation, catalytic hydrogenation, etc.

Among others, catalytic hydrogenation is preferable.

The catalytic hydrogenation is carried out in the  
25 presence of a catalyst such as palladium carbon, preferably 10% palladium carbon.

The catalytic hydrogenation is usually carried out in a conventional solvent such as tetrahydrofuran, ethanol, ethyl acetate, and other solvent which does not adversely affect  
30 the reaction, or a mixture thereof.

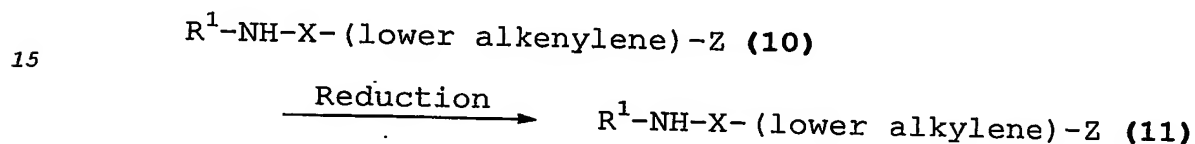
The catalytic hydrogenation is also preferably carried out in the presence of a conventional acid such as acetic acid, hydrochloric acid and the like. A liquid acid can be

also used as the solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

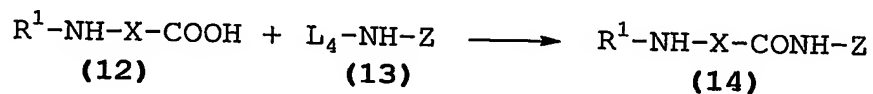
Compound (9) thus obtained can be isolated or purified  
 5 by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt same as those exemplified for Compound (I).

10 Therefore, Compound (11) or a salt thereof can be prepared from Compound (10) or a salt thereof in a similar manner as described above. Suitable salts of Compounds (10) and (11) may be the same as those exemplified for Compound (I).



The nitrogen atom in Compound (6), (7), (8), (9), (10) or (11) may be protected or deprotected, as necessary, in accordance with methods known *per se* such as the methods described in Protective Groups in Organic Synthesis,  
 20 published by John Wiley and Sons (1980), and the like.

**Procedure C:** Synthesis of Compound (I) wherein Y is -CONH-



wherein

25  $L_4$  is a hydrogen atom or a protecting group, which is known *per se*, such as tert-butoxycarbonyl as described in the above "optionally protected amino" (see Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), etc.); and

30  $R^1$ , X and Z are as defined above.

Amidation

Compound (12) or a reactive derivative thereof, or its salt is reacted with Compound (13) or its salt to give an  
5 amidated compound (14).

Suitable reactive derivative of Compound (12) includes an acid halide, an acid anhydride and an activated ester.

The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted  
10 phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid,  
15 ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole,  
20 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl  $[(CH_3)_2N^+=CH-]$  ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl  
25 ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranlyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); or an ester with an N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-  
30 hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.). These reactive derivatives can be optionally selected from them according to the kind of

Compound (12) to be used.

Suitable salts of Compound (12) and a reactive derivative thereof as well as Compound (13) may be the same as those exemplified for Compound (I).

5       Compound (12) and a reactive derivative thereof as well as Compound (13) or salts thereof may be commercially available or can be prepared in accordance with the methods known *per se* (see Production Example 7).

10       The conventional amidation method may be employed in the present invention.

The reaction is usually carried out in a conventional solvent such as dichloromethane, methanol, ethanol, acetone, tetrahydrofuran, N,N-dimethylformamide, and any other organic solvent which does not adversely influence the  
15       reaction, or a mixture thereof.

The reaction is also preferably carried out in the presence of a conventional condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, N,N'-dicyclohexylcarbodiimide, N,N'-carbonylbis(2-methylimidazole)triphenylphosphine, and an additive such as  
20       1-hydroxybenzotriazole, 1-hydroxysuccinimide, 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

25       Compound (14) thus obtained can be isolated or purified by known separation or purification means, such as concentration, concentration *in vacuo*, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like, and can be converted to a salt  
30       same as those exemplified for Compound (I).

The nitrogen atom in Compound (12), (13) or (14) may be protected or deprotected, as necessary, in accordance with methods known *per se* such as the methods described in

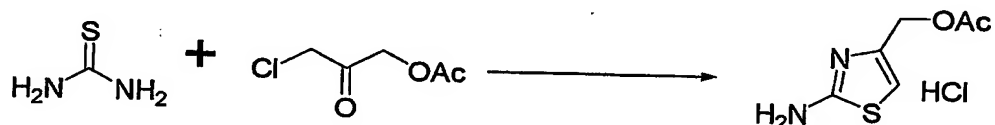
Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980), and the like.

The present invention is explained in more detail in the following by way of Production Examples and Examples, which  
5 are not to be construed as limitative.

The test compounds used in the Examples were N-{4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-  
yl}acetamide (hereinafter Compound A) synthesized in  
Production Example 1 and N-[4-(2-{4-  
10 [(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide  
(hereinafter Compound B) synthesized in Production Example 16.

### Production Example 1:

#### Step 1

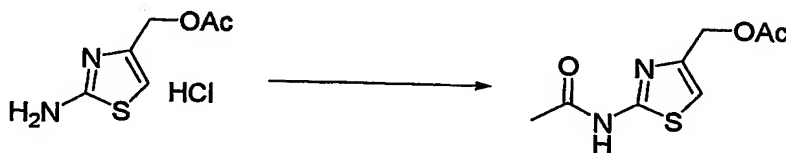


15 A mixture of 3-chloro-2-oxopropyl acetate (5 g) and thiourea (2.5 g) in ethanol (25 ml) was refluxed for 4 hours. The reaction mixture was cooled to ambient temperature and the resulting crystalline precipitate was collected by filtration and washed with ethanol (20 ml) to give (2-amino-1,3-thiazol-  
20 4-yl)methyl acetate hydrochloride (3.5 g) as white crystals.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.07 (3H, s), 4.92 (2H, s), 6.87 (1H, s).

MS: 173 (M+H)<sup>+</sup>

#### Step 2



25 To a mixture of (2-amino-1,3-thiazol-4-yl)methyl acetate hydrochloride (56 g) and pyridine (45 g) in dichloromethane

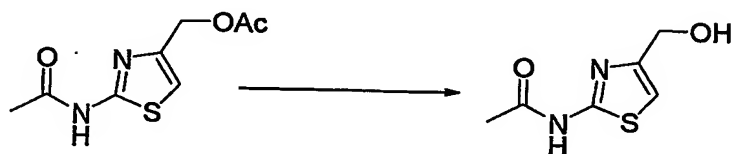
(560 ml) was added acetyl chloride (23 g) over a period of 30 minutes at 5°C, and the reaction mixture was stirred for 10 minutes at the same temperature. The reaction mixture was poured into water (500 ml) and extracted with chloroform (1 L).

5 The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residual solid was collected by filtration with isopropyl ether to give (2-(acetylamino)-1,3-thiazol-4-yl)methyl acetate (47 g) as white crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.12(3H, s), 2.29(3H, s), 5.08(2H, s),  
10 6.93(1H, s).

MS: 215(M+H)<sup>+</sup>

### Step 3

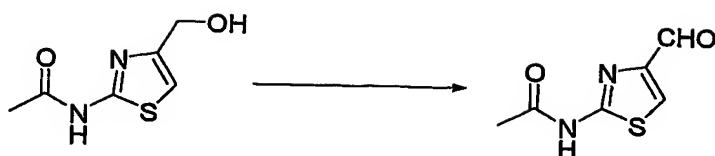


15 A mixture of (2-(acetylamino)-1,3-thiazol-4-yl)methyl acetate (46 g) and potassium carbonate (30 g) in methanol (640 ml) was stirred for 3 hours at ambient temperature. The reaction mixture was concentrated *in vacuo*. The residue was diluted with chloroform, and the insoluble material was  
20 filtered off. The resulting solution was purified by flash column chromatography on silica-gel with methanol / chloroform (1/99). The resulted solid was collected by filtration with isopropyl ether to give N-(4-(hydroxymethyl)-1,3-thiazol-2-yl)acetamide (35 g) as white crystals.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12(3H, s), 4.44(2H, d, J=5.0Hz), 5.20(1H, t, J=5.0Hz), 6.88(1H, s), 12.02(1H, brs).

MS: 173(M+H)<sup>+</sup>

### Step 4

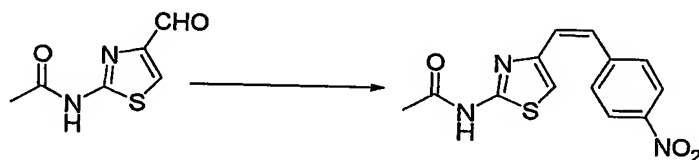


N-(4-(Hydroxymethyl)-1,3-thiazol-2-yl)acetamide (2.8 g) was dissolved in methanol (10 ml) and chloroform (200 ml). Then manganese (IV) oxide (28.3 g) was added to the solution under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 7 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The resulting solid was washed with ethyl ether to give N-(4-formyl-1,3-thiazol-2-yl)acetamide (2.01 g) as an off-white solid.

mp. 195.5-199°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17(3H, s), 8.28(1H, s), 9.79(1H, s), 12.47(1H, brs).

#### Step 5



1-(Bromomethyl)-4-nitrobenzene (1.9 g), triphenylphosphine (2.31 g) and N,N-dimethylformamide (20 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2.5 hours. Then potassium tert-butoxide (1.19 g) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (1.5 g) were added and the mixture was stirred at room temperature for 14 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with 1N-hydrochloric acid, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:1) → (1:2) as an eluent, and triturated with ethyl ether to give N-(4-[(Z)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl)acetamide (1.59 g) as a

yellow solid.

mp. 155-157°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.13 (3H, s), 6.64 (1H, d, J=12.5Hz),  
6.71 (1H, d, J=12.5Hz), 7.18 (1H, s), 7.79 (2H, d, J=9.0Hz),  
5 8.17 (2H, d, J=9.0Hz), 12.02 (1H, brs).

MS: 290 (M+H)<sup>+</sup>

#### Step 6



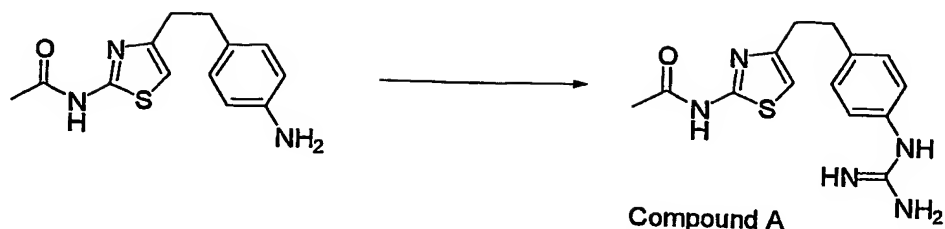
A mixture of N-{4-[(Z)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (2 g) and 10% palladium carbon (400 mg)  
10 in methanol (25 ml), tetrahydrofuran (25 ml) and acetic acid (18 ml) was stirred under 4 atm hydrogen at ambient temperature for 5 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate. The  
15 organic solution was washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:2) → ethyl  
20 acetate as an eluent, and triturated with ethyl alcohol / ethyl ether to give N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (539.6 mg) as an off-white solid.

mp. 102.5-104°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.75 (4H, brs), 4.82 (2H,  
25 s), 6.46 (2H, d, J=8.5Hz), 6.69 (1H, s), 6.83 (2H, d, J=8.5Hz), 12.07 (1H, brs).

MS: 262 (M+H)<sup>+</sup>

#### Step 7



To a suspension of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (26 g) in ethanol (500 ml) was added 4N hydrogen chloride in ethyl acetate (25 ml) and cyanamide (6.3 g). The mixture was refluxed for 26 hours. The reaction mixture was cooled to ambient temperature and poured into a mixture of ethyl acetate (500 ml) and saturated sodium hydrogen carbonate solution (500 ml). The resulted precipitate was collected by filtration and washed with water (300 ml) and ethanol (300 ml) to give N-{4-[2-(4-{[amino(imino)methyl]-amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (18 g) as white crystals.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.10 (3H, s), 2.85 (4H, s), 6.79 (1H, s), 6.83 (2H, d,  $J=7\text{Hz}$ ), 7.10 (2H, d,  $J=7\text{Hz}$ ).

MS: 304 ( $\text{M}+\text{H}$ ) $^+$

**Production Example 2:** Synthesis of N-(4-(2-(4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl)ethyl)-1,3-thiazol-2-yl)acetamide

N-(4-(2-(4-Aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (1.8 g) prepared in a similar manner according to Step 6 of Production Example 1, 2-(methylsulfanyl)-4,5-dihydro-1,3-thiazole (918 mg), hydrochloric acid concentrate (0.57 ml) and 2-methoxyethanol (28 ml) were combined under nitrogen atmosphere, and stirred at 120°C for 10 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran / water, and made basic with aqueous potassium carbonate. The mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, and evaporated *in vacuo*. The residue was purified by flash

column chromatography over silica gel with chloroform / methanol (30:1 → 20:1) as an eluent, and triturated with ethyl acetate to give N-(4-(2-(4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl)ethyl)-1,3-thiazol-2-yl)acetamide (484.7 mg) as an off-white solid.

mp. 218-219.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.84(4H, s), 3.26(2H, t, J=7.5Hz), 3.35(2H, t, J=7.5Hz), 4.02(1H, brs), 6.71(1H, brs), 7.05(2H, d, J=8.5Hz), 7.51(1H, brs), 9.25(1H, brs), 12.10(1H, brs).

MS: 347(M+H)<sup>+</sup>

**Production Example 3:** Synthesis of N-(4-{(E)-2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethenyl}-1,3-thiazol-2-yl)acetamide

**Step 1**

A mixture of 4-nitrobenzyl bromide (6.35 g), triphenylphosphine (7.71 g) and N,N-dimethylformamide (50 ml) was stirred for 5 hours at room temperature. To the mixture were added potassium butoxide (3.96 g), and then N-(4-formyl-1,3-thiazol-2-yl)acetamide (5.0 g) prepared in a similar manner according to Step 4 of Production Example 1, and the mixture was stirred for 13 hours at the same temperature. The reaction mixture was poured into ethyl acetate (200 ml) and water (200 ml). The organic layer was washed with water (20 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed with 30% ethyl acetate / diisopropyl ether to give N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (7.8 g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 7.29(1H, d, J=16Hz), 7.48(1H, d, J=16Hz), 7.88(2H, d, J=7Hz), 8.22(2H, d, J=7Hz).

MS (M+H)=290

**Step 2**

A mixture of N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-

thiazol-2-yl)acetamide (250 mg), palladium on carbon (25 mg) and methanol (2.5 ml) was stirred under hydrogen atmosphere for 2 hours at ambient temperature. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The

5 crystalline residue was collected and washed with isopropyl ether to give N-{4-[(E)-2-(4-aminophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (160 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.14 (3H, s), 5.33 (2H, s), 6.55 (2H, d, J=7Hz), 6.82 (1H, d, J=10Hz), 6.44 (1H, s), 7.09 (1H, d, J=10Hz), 7.20 (2H, d, J=7Hz).

10 MS: 260 (M+H)<sup>+</sup>

### Step 3

A mixture of N-{4-[(E)-2-(4-aminophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (200 mg), 2-(methylsulfanyl)-4,5-dihydro-1,3-thiazole (103 mg), hydrochloric acid (0.064 ml) and 2-methoxyethanol (2 ml) was stirred at 120°C for 8 hours. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica-gel flash column chromatography with hexane:ethyl acetate (3:1) as an eluent. The crystalline

20 residue was collected and washed with ethyl acetate to give N-(4-{(E)-2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethenyl}-1,3-thiazol-2-yl)acetamide (150 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.27 (3H, s), 3.33-3.40 (2H, m), 3.57-3.65 (2H, m), 6.94 (1H, s), 7.05 (1H, d, J=12Hz), 7.29 (1H, d, J=12Hz), 7.30 (2H, d, J=7Hz), 7.57 (2H, d, J=7Hz).

25 MS: 345 (M+H)<sup>+</sup>

**Production Example 4:** Synthesis of methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydriodide

### 30 Step 1

To an ice-cold solution of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (300 mg) prepared in a similar manner according to Step 6 of Production Example 1 in acetone

(5 ml) was added benzoyl isothiocyanate (187 mg) and the mixture was refluxed for 2 hours. The reaction mixture was cooled to 0°C. The precipitated crystals were filtered and washed with ice-cold acetone to give N-{4-[2-(4-

5 {[(benzoylamino)carbonothioyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (359 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.25(3H, s), 2.90-3.05(4H, m), 6.51(1H, s), 7.21(2H, d, J=7Hz), 7.50-7.70(5H, m), 7.89(2H, d, J=7Hz), 9.03(1H, s), 9.12(1H, s).

10 MS (M+H)=425

### Step 2

A mixture of N-{4-[2-(4-{[(benzoylamino)carbonothioyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (200 mg), 6N aqueous sodium hydroxide (0.19 ml) and ethanol (2 ml) was  
15 stirred at 60°C for 2 hours. The reaction mixture was cooled to ambient temperature and neutralized with 1N hydrochloric acid (1.2 ml). The precipitated crystals were filtered and washed with water to give N-[4-(2-{4-[(aminocarbonothioyl)-amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (120 mg).

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.88(4H, s), 6.75(1H, s), 7.15(2H, d, J=7Hz), 7.27(2H, d, J=7Hz), 9.60(1H, s).

MS (M+H)=321

### Step 3

A mixture of N-[4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (100 mg), methyl  
25 iodide (0.023 ml) and methanol (2 ml) was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and stirred for 30 minutes. The precipitated crystals were filtered and washed  
30 with ethyl acetate to give methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydriodide (130 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.13(3H, s), 2.68(3H, s), 2.87-

3.05 (4H, m), 6.75 (1H, s), 7.24 (2H, d, J=7Hz), 7.35 (2H, d, J=7Hz).

MS (M+H)=463

**Production Example 5:** Synthesis of N-(4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

A mixture of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (65 mg) prepared in a similar manner according to Step 6 of Production Example 1, ethyl 2-(methylsulfanyl)-4,5-dihydro-1H-imidazole-1-carboxylate (56 mg), acetic acid (0.1 ml), ethanol (0.9 ml) was stirred at 65°C for 6 hours, and then refluxed for 5 hours. The reaction mixture was poured into ethyl acetate (5 ml) and saturated aqueous sodium bicarbonate. The precipitated solid was filtered, and the solid was dissolved in 50% methanol/chloroform. The insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The solid residue was collected and washed with ethyl acetate to give N-(4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (40 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.72 (4H, s), 3.33 (4H, s), 6.73 (1H, s), 6.85-7.08 (4H, m).

MS (M+H)=330

**Production Example 6:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}-2-methylpropanamide

**Step 1**

To an ice-cold mixture of ethyl 2-amino-1,3-thiazole-4-carboxylate (2 g) prepared in a similar manner according to Step 1 of the following Production Example 7, pyridine (1.3 ml) and dichloromethane (20 ml) was added isobutyryl chloride (0.91 ml) and stirred for 30 minutes. To the mixture was added saturated aqueous hydrogen bicarbonate (30 ml), and the organic layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected

and washed with ethyl acetate to give ethyl 2-(isobutyrylamino)-1,3-thiazole-4-carboxylate (1.34 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.30 (6H, d, J=7Hz), 1.40 (3H, t, J=7Hz), 2.57-2.73 (1H, m), 4.41 (2H, q, J=7Hz), 7.83 (1H, s),  
5 8.98 (1H, s).

MS: 243 (M+H)<sup>+</sup>

### Step 2

To a mixture of ethyl 2-(isobutyrylamino)-1,3-thiazole-4-carboxylate (1.4 g) and tetrahydrofuran (28 ml) was added  
10 lithium borohydride (252 mg) portionwise, and the mixture was refluxed for 6 hours. The reaction mixture was cooled to 0°C, quenched with methanol (5 ml) and concentrated *in vacuo*. The residue was suspended with 10% methanol / chloroform (100 ml), and the insoluble materials were filtered off. The filtrate  
15 was purified by flash column chromatography on silica-gel with 5% methanol / chloroform as an eluent. The crystalline residue was collected and washed with diisopropyl ether to give N-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-2-methylpropanamide (1.0 g).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.32 (6H, d, J=5Hz), 2.58-2.73 (1H, m),  
20 4.68 (2H, s), 6.82 (1H, s).

MS (M+H)=200

### Step 3

A mixture of N-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-2-methylpropanamide (520 mg), manganese (IV) oxide (2.26 g),  
25 methanol (0.5 ml) and chloroform (5 ml) was stirred at ambient temperature for 18 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The crystalline residue was collected and washed with diisopropyl ether to give N-(4-formyl-1,3-thiazol-2-yl)-2-methylpropanamide (365 mg).  
30

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.13 (6H, d, J=5Hz), 2.60-2.77 (1H, m), 7.86 (1H, s).

MS (M+H)=199

Step 4

A mixture of 4-nitrobenzyl bromide (381 mg), triphenylphosphine (463 mg) and N,N-dimethylformamide (3 ml) was stirred for 5 hours at room temperature. To the mixture were added potassium butoxide (238 mg) and then N-(4-formyl-1,3-thiazol-2-yl)-2-methylpropanamide (350 mg), and the mixture was stirred for 13 hours at the same temperature. The reaction mixture was poured into ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with water (20 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed to give 2-methyl-N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}propanamide (360 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta$  (ppm): 1.25(6x2/3H, d, J=5Hz), 1.30(6x1/3H, d, J=5Hz), 2.50-5.70(1H, m), 6.63(1H, s), 6.79(1x2/3H, s), 6.97(1x2/3H, s), 7.14(1x1/3H, d, J=12Hz), 7.33(1x1/3H, d, J=12Hz), 7.53(2x2/3H, d, J=7Hz), 7.62(2x1/3H, d, J=7Hz), 8.13(2x2/3H, d, J=7Hz), 8.22(2x1/3H, d, J=7Hz).

MS (M+H)=318

Step 5

A mixture of 2-methyl-N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}propanamide (333 mg), palladium on carbon (33 mg), acetic acid (1 ml), methanol (2 ml) and tetrahydrofuran (2 ml) was stirred under hydrogen atmosphere (4 atm) at ambient temperature for 5 hours. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with 5% methanol / ethyl acetate as an eluent. The solid residue was collected and washed with diisopropyl ether to give N-{4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-yl}-2-methylpropanamide (260 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta$  (ppm): 1.38(6H, d, J=5Hz), 2.57-2.73(1H, m), 2.39-2.43(4H, m), 6.45(1H, s), 6.62(2H, d, J=7Hz), 6.97(2H, d,

J=7Hz) .

MS (M+H)=290

Step 6

The title compound was prepared in a similar manner  
5 according to Step 7 of Production Example 1.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.01(6H, d, J=5Hz), 2.62-2.78(1H, m), 2.83(4H, s), 6.72(2H, d, J=7Hz), 6.75(1H, s), 7.04(2H, d, J=7Hz) .

MS (M+H)=332

10 Production Example 7: Synthesis of 2-(acetylamino)-N-(4-  
{[amino(imino)methyl]amino}phenyl)-1,3-thiazole-4-carboxamide  
Step 1

A mixture of ethyl 3-bromo-2-oxopropanoate (100 g),  
thiourea (39 g) and ethanol (500 ml) was refluxed for 2 hours.

15 The reaction mixture was concentrated *in vacuo*. The  
crystalline residue was collected and washed with ethyl  
acetate to give ethyl 2-amino-1,3-thiazole-4-carboxylate  
hydrobromide (116 g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.28(3H, t, J=7Hz), 4.26(2H, q,  
20 J=7Hz), 7.60(1H, s).

Step 2

To an ice-cold mixture of ethyl 2-amino-1,3-thiazole-4-  
carboxylate hydrobromide (80 g), pyridine (52.5 g) and  
dichloromethane (800 ml) was added acetyl chloride (27.3 g)  
25 dropwise at 0°C, and the mixture was stirred for 30 minutes at  
the same temperature. The reaction mixture was washed with  
water (500 ml), dried over sodium sulfate and concentrated *in*  
*vacuo*. The crystalline residue was collected and washed with  
ethyl acetate to give ethyl 2-(acetylamino)-1,3-thiazole-4-  
30 carboxylate (60 g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.29(3H, t, J=7Hz), 2.15(3H, s),  
4.27(2H, q, J=7Hz), 8.03(1H, s).

MS (M+H)=215

Step 3

A mixture of ethyl 2-(acetylamino)-1,3-thiazole-4-carboxylate (2 g), 2N sodium hydroxide (7 ml) and methanol (13 ml) was stirred at ambient temperature for 5 hours. The  
5 reaction mixture was neutralized by 1N hydrochloric acid (14 ml). The precipitated crystals were filtered and washed with water to give 2-(acetylamino)-1,3-thiazole-4-carboxylic acid (1.3 g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.14 (3H, s), 7.94 (1H, s).

10 Step 4

A mixture of 2-(acetylamino)-1,3-thiazole-4-carboxylic acid (500 mg), tert-butyl 4-aminophenylcarbamate (615 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (566 mg), 1-hydroxybenzotriazole (399 mg) and dichloromethane (5  
15 ml) was stirred at ambient temperature for 3 hours. The reaction mixture was washed with saturated aqueous sodium hydrogen bicarbonate, and the organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with 3% methanol / chloroform as  
20 an eluent. The crystalline residue was collected and washed with ethyl acetate to give tert-butyl 4-([2-(acetylamino)-1,3-thiazol-4-yl]carbonyl)amino)phenylcarbamate (580 mg).  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>); δ (ppm): 1.48 (9H, s), 2.18 (3H, s), 7.42 (2H, d, J=7Hz), 7.61 (2H, d, J=7Hz), 7.91 (1H, s), 9.32 (1H, s),  
25 9.63 (1H, s).

MS (M+H)=377

Step 5

To a solution of tert-butyl 4-([2-(acetylamino)-1,3-thiazol-4-yl]carbonyl)amino)phenylcarbamate (85 mg) in  
30 methanol (1 ml) was added 4N hydrogen chloride in ethyl acetate (1 ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The solid residue was collected and washed with

ethyl acetate to give 2-(acetylamino)-N-(4-aminophenyl)-1,3-thiazole-4-carboxamide hydrochloride (70 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 7.42(2H, d, J=7Hz), 7.37(2H, d, J=7Hz), 7.41(1H, s).

5 MS (M+H)=313

#### Step 6

A mixture of 2-(acetylamino)-N-(4-aminophenyl)-1,3-thiazole-4-carboxamide hydrochloride (70 mg), cyanamide (11 mg) and 2-methoxyethanol (2 ml) was stirred at 100°C for 72  
10 hours. The reaction mixture was concentrated *in vacuo*. To the residue was added ethyl acetate (5 ml) and saturated aqueous sodium hydrogen bicarbonate (5 ml). The precipitated solid was filtered and washed with ethyl acetate and water to give 2-(acetylamino)-N-(4-{[amino(imino)methyl]amino}phenyl)-1,3-  
15 thiazole-4-carboxamide (45 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 7.60-7.88(4H, br), 7.95(1H, s).

MS (M+H)=319

#### Production Example 8: Synthesis of N-(4-{2-[4-

20 (ethanimidoylamino)phenyl]ethyl)-1,3-thiazol-2-yl)acetamide

N-(4-(2-(4-Aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (100 mg) prepared in a similar manner according to Step 6 of Production Example 1, methyl ethanimidothioate hydriodide (166 mg) and methanol (3 ml) were combined, and refluxed for 1.5  
25 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography over NH silica gel with chloroform / methanol (20:1 → 10:1) as an eluent to give N-(4-{2-[4-(ethanimidoylamino)phenyl]ethyl)-1,3-thiazol-2-yl)acetamide  
30 (165 mg) as a pale yellow amorphous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.03(3H, brs), 2.19(3H, s), 2.92(4H, s), 6.47(1H, s), 6.78(2H, d, J=8.0Hz), 7.08(2H, d, J=8.0Hz).

MS: 303(M+H)<sup>+</sup>

**Production Example 9:** Synthesis of N-[4-(2-{4-[amino(imino)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide hydrochloride

Step 1

5 4-(Bromomethyl)benzonitrile (1.73 g), triphenylphosphine (2.31 g) and N,N-dimethylformamide (20 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours. Then potassium tert-butoxide (1.19 g) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (1.5 g) prepared  
10 in a similar manner according to Step 4 of Production Example 1 were added to the mixture, and stirred at room temperature for 3 hours. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with 1N-hydrochloric acid, water and saturated sodium chloride  
15 solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:1) as an eluent, and triturated with ethyl ether to give a mixture of N-{4-[(Z)-2-(4-cyanophenyl)ethenyl]-1,3-  
20 thiazol-2-yl}acetamide and N-{4-[(E)-2-(4-cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (Z : E = 3 : 1) (1.63 g) as a pale yellow solid.

mp. 175-176°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.13(3Hx3/4, s), 2.16(3Hx1/4, s),  
25 6.59(1Hx3/4, d, J=13.0Hz), 6.65(1Hx3/4, d, J=13.0Hz),  
7.11(1Hx3/4, s), 7.24(1Hx1/4, d, J=16.0Hz), 7.28(1Hx1/4, s),  
7.40(1Hx1/4, d, J=16.0Hz), 7.65(2Hx3/4, d, J=8.5Hz),  
7.74(2Hx1/4, d, J=8.5Hz), 7.75(2Hx3/4, d, J=8.5Hz),  
7.83(2Hx1/4, d, J=8.5Hz), 12.00(1H, brs).

30 MS: 270(M+H)<sup>+</sup>

Step 2

A mixture of N-{4-[(Z)-2-(4-cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide and N-{4-[(E)-2-(4-

cyanophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (Z : E = 3 : 1) (1.5 g), 10% palladium on carbon (323 mg), methanol (20 ml), tetrahydrofuran (10 ml) and acetic acid (5 ml) were combined. The reaction mixture was stirred under 4 atm hydrogen at ambient temperature for 9 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (1:1) → chloroform / methanol (30:1) as an eluent, and triturated with ethyl ether to give N-{4-[2-(4-cyanophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (1.18 g) as a colorless solid.

mp. 205-206.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.90(2H, t, J=8.0Hz), 3.01(2H, t, J=8.0Hz), 6.73(1H, s), 7.40(2H, d, J=8.0Hz), 7.74(2H, d, J=8.0Hz), 12.09(1H, brs).

MS: 272 (M+H)<sup>+</sup>

### Step 3

N-{4-[2-(4-Cyanophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (600 mg) was dissolved in ethanol (5 ml) and chloroform (5 ml), and then hydrochloric acid gas was bubbled at 0°C for 5 minutes with stirring. The reaction mixture was stood for 15 hours, and concentrated *in vacuo*. The residual solid was washed with diethyl ether to give ethyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzenecarboximidoate hydrochloride (924.7 mg) as a pale green solid.

mp. 129-130°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.48(3H, t, J=7.0Hz), 2.12(3H, s), 2.95(2H, t, J=8.0Hz), 3.07(2H, t, J=8.0Hz), 4.61(2H, q, J=7.0Hz), 6.72(1H, s), 7.46(2H, d, J=8.5Hz), 8.02(2H, d, J=8.5Hz), 11.25(1H, brs), 11.98(1H, brs), 12.11(1H, brs).

MS: 318 (M+H)<sup>+</sup> free

### Step 4

Ethyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-

yl]ethyl}benzenecarboximidoate hydrochloride (300 mg) was dissolved in ethanol (6 ml). Then ammonium chloride (68 mg) and ammonia in methanol (1 ml) were added to the solution. The reaction mixture was refluxed for 5 hours under nitrogen atmosphere. After cooled to room temperature, the suspension was filtered *in vacuo*. The filtrate was concentrated *in vacuo*, and the residue was solidified with ethanol / diethyl ether to give N-[4-(2-{4-[amino(imino)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide hydrochloride (234 mg) as a colorless solid.  
mp. 229.5-231°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12(3H, s), 2.94(2H, t, J=8.0Hz), 3.06(2H, t, J=8.0Hz), 6.75(1H, s), 7.44(2H, d, J=8.5Hz), 7.76(2H, d, J=8.5Hz), 12.10(1H, brs).

MS: 289(M+H)<sup>+</sup> free

**Production Example 10:** Synthesis of N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)-2-[[amino(imino)methyl]amino]-acetamide hydrochloride

Step 1

A mixture of N-(4-(2-(4-aminophenyl)ethyl)-1,3-thiazol-2-yl)acetamide (100 mg) prepared in a similar manner according to Step 6 of Production Example 1, ((tert-butoxycarbonyl)amino)acetic acid (74 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (81 mg), 1-hydroxybenzotriazole (57 mg) and dichloromethane (5 ml) was stirred at ambient temperature for 3 hours. The reaction mixture was washed with saturated aqueous sodium hydrogen bicarbonate, and the organic layer was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica-gel with 3% methanol / chloroform as an eluent. The crystalline residue was collected and washed with ethyl acetate to give tert-butyl 2-[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]-2-oxoethylcarbamate (580 mg).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.47(9H, s), 2.25(3H, s), 2.92(4H, s),

3.92 (2H, d, J=5Hz), 6.46 (1H, s), 7.10 (2H, d, J=7Hz), 7.38 (2H, d, J=7Hz).

MS (M+H)=419

### Step 2

5 To a solution of tert-butyl 2-[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]-2-oxoethylcarbamate (100 mg) in ethyl acetate (1 ml) was added 4N hydrogen chloride in ethyl acetate (1 ml), and the mixture was stirred at ambient temperature for 103 hours. The precipitated solid was filtered  
10 and washed with ethyl acetate to give N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)-2-aminoacetamide hydrochloride (80 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.87 (4H, s), 6.70 (1H, s), 7.17 (2H, d, J=7Hz), 7.49 (2H, d, J=7Hz).

15 MS (M+H)=319

### Step 3

The title compound was prepared in a similar manner according to Step 7 of Production Example 1.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.80-2.95 (4H, m),  
20 3.76 (2H, s), 6.70 (1H, s), 7.26 (2H, d, J=7Hz), 7.49 (2H, d, J=7Hz), 8.16 (2H, s).

MS (M+H)=361

**Production Example 11:** Synthesis of N-{4-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]-1,3-thiazol-2-  
25 yl}acetamide hydrochloride

### Step 1

Aluminium chloride (1.63 g) was dissolved in 1,2-dichloroethane (15 mL). Chloroacetylchloride (0.732 mL) was added to the mixture at 0°C, and stirred  
30 additionally for 20 minutes, then N-(2-phenylethyl)acetamide (1 g) in 1,2-dichloroethane (5 mL) was added dropwise. The mixture was stirred for 1 hour at room temperature, and then poured into ice-water. The mixture was extracted with

chloroform, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo*. The solid was washed with ethyl acetate and ethyl ether, and dried *in vacuo* to give N-{2-[4-(2-chloroacetyl)phenyl]ethyl}-  
5 acetamide as a white powder (1.18 g, 80.4%).

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 7.92 (2H, d, J=6Hz), 7.34 (2H, d, J=6Hz), 5.66 (1H, br), 4.70 (2H, s), 3.55-3.60 (2H, m), 2.90-2.94 (2H, m), 1.98 (3H, s).

#### Step 2

10 N-{2-[4-(2-Chloroacetyl)phenyl]ethyl}acetamide (1.06 g) and thiourea (505 mg) were dissolved in ethanol (20 mL). The mixture was refluxed for 1 hour and allowed to cool to room temperature. The white solid was collected with filtration and washed with ethanol to give N-{2-[4-(2-amino-1,3-thiazol-4-  
15 yl)phenyl]ethyl}acetamide hydrochloride (1.19 g, 90.4%).

MS m/z 262 (M++1).

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 7.93-7.96 (2H, m), 7.69 (2H, d, J=6Hz), 7.30 (2H, d, J=6Hz), 7.16 (1H, s), 3.23-3.30 (2H, m), 2.70-2.76 (2H, m), 1.78 (3H, s).

#### 20 Step 3

N-{2-[4-(2-Amino-1,3-thiazol-4-yl)phenyl]ethyl}acetamide (0.6 g) was dissolved in ethanol (10 mL) and hydrochloric acid concentrate (10 mL). The mixture was refluxed for 5 hours. The solvent was evaporated *in vacuo*. The residue was washed  
25 with ethyl ether to give 4-[4-(2-aminoethyl)phenyl]-1,3-thiazol-2-amine dihydrochloride (0.5 g, 84.6%).

MS m/z 220 (M++1).

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 8.15 (3H, br), 7.78 (2H, d, J=6Hz), 7.39 (2H, d, J=6Hz), 7.24 (1H, s), 3.03-3.10 (2H, m),  
30 2.90-2.98 (2H, m).

#### Step 4

4-[4-(2-Aminoethyl)phenyl]-1,3-thiazol-2-amine dihydrochloride (0.45 g) was dissolved in 1,4-dioxane (10 mL),

water (3 mL) and 1N sodium hydroxide solution (3.1 mL). Di-tert-butyl dicarbonate (336 mg) was added at 0°C. The mixture was stirred at room temperature overnight, then extracted with ethyl acetate, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo*. The solid was washed with ethyl ether, and dried *in vacuo* to give tert-butyl {2-[4-(2-amino-1,3-thiazol-4-yl)phenyl]ethyl}-carbamate as a white solid (311 mg, 63.2%).

MS m/z 320 (M++1).

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 7.69(2H, d, J=6Hz), 7.18(2H, d, J=6Hz), 7.02(2H, br), 7.69(1H, s), 3.10-3.27(2H, m), 2.65-2.72(2H, m), 1.37(9H, s).

#### Step 5

tert-Butyl {2-[4-(2-amino-1,3-thiazol-4-yl)phenyl]ethyl}carbamate (290 mg) was dissolved in dichloromethane (5 mL), then acetic anhydride (0.103 mL), 4-dimethylaminopyridine (10 mg) and pyridine (0.147 mL) were added. The mixture was stirred overnight. The mixture was extracted with chloroform, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo*. The solid was washed with ethyl ether, and dried *in vacuo* to give tert-butyl (2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)carbamate as a white solid (280 mg, 85.3%).

MS m/z 362 (M++1).

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 7.80(2H, d, J=6Hz), 7.53(1H, s), 7.24(2H, d, J=6Hz), 6.90(1H, m), 3.12-3.18(2H, m), 2.16-2.63(2H, m), 2.16(3H, s), 1.37(9H, s).

#### Step 6

tert-Butyl (2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)carbamate (250 mg) was dissolved in ethyl acetate (4 mL) and 4 N hydrogen chloride in ethyl acetate (2 mL). The solvent was evaporated *in vacuo*. The solid was

washed with ethyl acetate and ethyl ether to give N-{4-[4-(2-aminoethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride (220 mg, 106%).

MS m/z 262 (M++1).

<sup>5</sup> <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 8.05(3H, br), 7.85(2H, d, J=6Hz), 7.58(1H, s), 7.32(2H, d, J=6Hz), 3.12-3.18(2H, m), 2.88-2.94(2H, m), 2.16(3H, s).

#### Step 7

N-{4-[4-(2-Aminoethyl)phenyl]-1,3-thiazol-2-yl}acetamide  
<sup>10</sup> hydrochloride (200 mg) and diisopropylethylamine (0.175 mL) were dissolved in tetrahydrofuran (5 mL). The mixture was stirred at room temperature overnight, then evaporated *in vacuo*. The residue was purified with silica gel chromatography (5% methanol / chloroform) to give di-tert-butyl {[2-{4-[2-(acetylamino)-1,3-thiazol-4-  
<sup>15</sup> yl]phenyl}ethyl)amino]methylidene}-biscarbamate (268 mg, 79.2%).

MS m/z 504 (M++1).

#### Step 8

<sup>20</sup> Di-tert-butyl {[2-{4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)amino]methylidene}biscarbamate (268 mg, 79.2%) (170 mg) was dissolved in 4 N hydrogen chloride in 1,4-dioxane (5 mL). The mixture was stirred at room temperature for 2 days, and then evaporated *in vacuo*. The residue was washed  
<sup>25</sup> with ethyl ether, dried *in vacuo* to give N-{4-[4-(2-{[amino(imino)methyl]amino}ethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride (50 mg, 43.6%).

MS m/z 304 (M++1).

<sup>30</sup> <sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>), δ (ppm): 7.83(2H, d, J=8Hz), 7.62-7.66(1H, m), 7.56(1H, s), 7.34(2H, d, J=8Hz), 3.37-3.45(2H, m), 2.78-2.85(2H, m), 2.16(3H, s).

**Production Example 12:** Synthesis of N-(4-{2-[4-(aminomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

Step 1

To a mixture of N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (50 mg) prepared in a similar manner according to Step 3 of the following Production Example  
5 16, carbon tetrabromide (72 mg) and dichloromethane (1 ml) was added triphenylphosphine (71 mg), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was purified by flash column chromatography on silica gel with 1% methanol / chloroform as an eluent. The crystalline residue  
10 was collected and washed with diisopropyl ether to give N-(4-{2-[4-(bromomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (48 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.25 (3H, s), 2.85-3.03 (4H, m),  
4.49 (2H, s), 6.48 (1H, s), 7.13 (2H, d, J=7Hz), 7.30 (2H, d,  
15 J=7Hz).

MS (M+H)=339

Step 2

To a mixture of N-(4-{2-[4-(bromomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (100 mg), tetrahydrofuran (2 ml)  
20 and N,N-dimethylformamide (2 ml) was added sodium diformylimide (42 mg), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with water (3 ml), and the precipitated solid was filtered and washed with water to give N-[4-(2-{4-[(diformylamino)-  
25 methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (80 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.23 (3H, s), 2.83-3.00 (4H, m),  
4.72 (2H, s), 6.48 (1H, s), 7.10 (2H, d, J=7Hz), 7.38 (2H, d,  
J=7Hz).

MS (M+H)=318

Step 3

To a solution of N-[4-(2-{4-[(diformylamino)methyl]-phenyl}ethyl)-1,3-thiazol-2-yl]acetamide (56 mg) in methanol (0.5 ml) was added 4N hydrogen chloride in ethyl acetate (0.5

ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The residue was separated between chloroform (5 ml) and saturated aqueous sodium hydrogen bicarbonate (5 ml), and the aqueous layer was extracted with chloroform (5 ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give N-(4-{2-[4-(aminomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (50 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12 (3H, s), 2.80-3.00 (4H, m), 3.92-4.05 (2H, m), 6.72 (1H, s), 7.24 (2H, d, J=7Hz), 7.37 (2H, d, J=7Hz).

MS (M+H)=276

**Production Example 13:** Synthesis of ethyl 4-[2-(4-[[amino(imino)methyl]amino]phenyl)ethyl]-1,3-thiazol-2-ylcarbamate hydrochloride

**Step 1:** ethyl 4-(hydroxymethyl)-1,3-thiazol-2-ylcarbamate

A mixed solution of ethyl 4-(chloromethyl)-1,3-thiazol-2-ylcarbamate (500 mg) in 1,4-dioxane (5 ml) and water (10 ml) was refluxed with stirring for 3.5 hours. After cooling, it was concentrated under reduced pressure. The mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless syrup (450 mg, 98.2%).

MS (ES+); 203 (M+H)<sup>+</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.39 (3H, t, J=7.0Hz), 4.39 (2H, q, J=7.0Hz), 4.61 (2H, s), 6.80 (1H, s).

**Step 2:** ethyl 4-formyl-1,3-thiazol-2-ylcarbamate

To a mixed solution of ethyl 4-(hydroxymethyl)-1,3-

thiazol-2-ylcarbamate (446 mg) in chloroform (30 ml) and methanol (3 ml) was added portionwise manganese (IV) oxide chemicals treated (1.92 g) at room temperature. After the mixture was stirred at the same temperature for 2 hours, then  
5 treated manganese (IV) oxide chemicals (250 mg) was added again to the solution, and it was stirred at 50°C for 3 hours. Manganese (IV) oxide was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g)  
10 using a mixed solvent of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless powder (470 mg, 106.4%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.36(3H, t, J=7.0Hz), 4.34(2H, q, J=7.0Hz), 7.83(1H, s), 9.54(1H, br), 9.88(1H, s).

#### Step 3

Ethyl 4-[2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-ylcarbamate (E-Z mixture) was obtained in a similar manner according to Step 5 of Production Example 1.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) (cis-trans product mixture), δ (ppm): 1.20-1.40(3H, m), 4.20-4.40(2H, m), 6.60, 6.66(1.2H, ABq, J=13Hz), 6.74(0.6H, s), 6.94(0.4H, s), 7.12, 7.30(0.8H, ABq, J=16Hz), 7.53(1.2H, d, J=8.9Hz), 7.61(0.8H, d, J=8.9Hz), 8.11(1.2H, d, J=8.9Hz), 8.22(0.8H, d, J=8.9Hz).

#### 25 Step 4

Ethyl 4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-ylcarbamate was obtained in a similar manner according to Step 6 of Production Example 1.

MS (ES+); 292 (M+H)<sup>+</sup>

30 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.24(3H, t, J=7.1Hz), 2.65-2.80(4H, m), 4.18(2H, q, J=7.1Hz), 4.82(2H, br), 6.46(2H, d, J=8.5Hz), 6.69(1H, s), 6.84(2H, d, J=8.5Hz).

#### Step 5

Ethyl 4-[2-(4-{N',N''-bis(tert-butoxycarbonyl)-[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-ylcarbamate was obtained in a similar manner according to Step 3 of the following Production Example 14.

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.29(3H, t, J=7.0Hz), 1.40-1.70(18H, m), 2.94(4H, s), 4.27(2H, q, J=7.0Hz), 6.45(1H, s), 7.12(2H, d, J=8.4Hz), 7.48(2H, d, J=8.4Hz), 10.25(1H, s).

Step 6

The title compound was prepared in a similar manner according to Step 5 of the following Production Example 14.

MS (ES+); 334 (M+H)<sup>+</sup> free

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.24(3H, t, J=7.0Hz), 2.80-3.00(4H, m), 4.19(2H, q, J=7.0Hz), 6.76(1H, s), 7.14(2H, d, J=8.4Hz), 7.28(2H, d, J=8.4Hz), 7.46(3H, br), 9.91(1H, s).

15 Production Example 14: Synthesis of N-{4-[2-(3-[[amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1: N-{4-[2-(3-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (E-Z mixture)

20 To a solution of 1-(bromomethyl)-3-nitrobenzene (276 mg) in N,N-dimethylformamide (7 mL) was added triphenylphosphine (335 mg) at room temperature. After the mixed solution was stirred for 4 hours, potassium tert-butoxide (172 mg) and N-(4-formyl-1,3-thiazol-2-yl)acetamide (217 mg) were  
25 successively added to the solution at the same temperature. After the whole solution was stirred at room temperature for 5 hours, the mixture was poured into water, the pH of the aqueous layer was adjusted to 7 with 1N-hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The  
30 extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of n-hexane and ethyl acetate (4:1). The

fractions containing the objective compound were collected and evaporated under reduced pressure to give brown powder of the title compound (E-Z mixture) (323 mg, 87.4%).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) (cis-trans product mixture), δ (ppm):

5 2.11(2.49H, s), 2.16(0.51H, s), 6.66(1.66H, s), 7.13(0.83H, s), 7.28(0.17H, s), 7.29, 7.46(0.34H, ABq, J=16Hz), 7.60(1H, t, J=7.9Hz), 7.91(0.83H, d, J=7.9Hz), 8.01(0.17H, d, J=7.9Hz), 8.09-8.13(1H, m), 8.28(0.83H, m), 8.38(0.17H, m).

10 Step 2: N-{4-[2-(3-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide

N-{4-[2-(3-Nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (E,Z mixture) (315 mg) in a mixed solvent of methyl alcohol (3 ml), tetrahydrofuran (6 ml), and acetic acid (1 ml) was hydrogenated over 10% Palladium on carbon (50% wet, 15 200 mg) under 4.3 atmospheric pressure at room temperature for 3 hours. The catalyst was removed off by filtration, and the filtrate was evaporated *in vacuo*. The residue was poured into water, the pH of the aqueous layer was adjusted to 9 with aqueous sodium hydrogen carbonate. The resulting mixture was 20 extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (9 g) using a mixed solvent of n-hexane and ethyl acetate (2:1 to 1:1). The fractions 25 containing the objective compound were collected and evaporated under reduced pressure to give syrup. The syrup of the objective compound was changed to solid in freezer (275 mg, 96.6%).

MS (ES+); 262 (M+H)<sup>+</sup>

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.23(3H, s), 2.80-3.00(4H, m), 3.60(2H, br), 6.51(1H, s), 6.45-6.65(3H, m), 7.06(1H, t, J=7.9Hz), 9.45(1H, br).

Step 3: N-{4-[2-(3-{[N',N''-bis(tert-butoxycarbonyl)amino-

(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

To a solution of N-{4-[2-(3-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (267 mg) in tetrahydrofuran (3 ml) was added N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-  
5 carboxamidine (317 mg) at room temperature. After the mixed solution was stirred for 3 days at the same temperature, and then evaporated under reduced pressure, the resulting residue was purified by column chromatography on silica gel (10 g) using a mixed solvent of n-hexane and ethyl acetate (4:1 to  
10 3:2). The fractions containing the objective compound were collected and evaporated under reduced pressure to give colorless foam of the title compound (316 mg, 61.4%).

MS (ES+); 504 (M+H)<sup>+</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.40-1.80(18H, m), 2.25(3H, s),  
15 2.97(4H, m), 6.37(1H, m), 6.53(1H, s), 6.91(1H, d, J=7.9Hz), 7.23(1H, t, J=7.9Hz), 7.34(1H, s), 7.52(1H, d, J=7.9Hz), 7.63-7.64(1H, m), 10.28(1H, s).

Step 4: N-{4-[2-(3-{[N',N''-bis(tert-butoxycarbonyl)amino-(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-  
20 yl}acetamide

To a suspension of N-{4-[2-(3-{[N',N''-bis(tert-butoxycarbonyl)amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (115 mg) in methanol (3 ml) was added N-bromosuccinimide (44.7 mg) at room temperature. After the  
25 mixed solution was stirred at the same temperature for 1 hour, the resulting precipitate was collected by filtration, washed with a mixed solvent of diisopropyl ether and n-hexane (1:1). The title compound was obtained as white powder (70 mg, 52.6%).

30 MS (ES+); 582 (M+H)<sup>+</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.40-1.75(18H, m), 2.21(3H, s), 2.85-3.00(4H, m), 6.93(1H, d, J=7.9Hz), 7.23(1H, t, J=7.9Hz), 7.30(1H, s), 7.51(1H, d, J=7.9Hz), 9.26(1H, br), 10.26(1H,

br), 11.63(1H, br).

#### Step 5

To a solution of N-{4-[2-(3-{[N',N''-bis(tert-butoxycarbonyl)amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-  
5 1,3-thiazol-2-yl}acetamide (64 mg) in dichloromethane (0.5 ml) was added dropwise 4N-hydrogen chloride in 1,4-dioxane (2 ml) at room temperature. After being stirred at the same temperature for 20 hours, the reaction mixture was concentrated under reduced pressure. The resulting residue was  
10 dissolved in a minimum methanol, and the solution was gradually diluted with ethyl acetate. The resulting precipitate was collected by filtration, washed with diisopropyl ether. The title compound was obtained as colorless powder (37 mg, 80.4%).

15 MS (ES+); 382 (M+H)<sup>+</sup> free

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.14(3H, s), 2.80-3.00(4H, m), 7.00-7.15(3H, m), 7.35(1H, t, J=7.9Hz), 7.51(4H, br), 10.01(1H, br), 12.42(1H, br).

**Production Example 15:** Synthesis of N-{4-[2-(4-  
20 {[amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide hydrochloride

#### Step 1-a

Di-tert-butyl {(4-{2-[2-(acetyl amino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
25 from the compound of Step 6 of Production Example 1 in a similar manner according to the following Step 5 of Production Example 18.

mp. 275.5-276°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.11(3H, s), 2.82-2.96(4H, m), 6.74(1H, s), 7.18(2H, d, J=8.5Hz),  
30 7.42(2H, d, J=8.5Hz), 9.94(1H, brs), 11.44(1H, brs), 12.09(1H, brs).

MS: 504 (M+H)<sup>+</sup>

Step 1-b

Di-tert-butyl {[ (4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (310 mg) prepared in a similar manner according to Step 5 of the following Production Example 18 was dissolved in methanol (6 ml) and tetrahydrofuran (3 ml) under nitrogen atmosphere. Then N-bromosuccinimide (164 mg) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 4 hours, and concentrated *in vacuo*. Chloroform and saturated sodium hydrogen carbonate solution were added to the residue. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / ethyl acetate (2:1) as an eluent to give di-tert-butyl {[ (4-{2-[2-(acetylamino)-5-bromo-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (271.4 mg) as a colorless amorphous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.22(3H, s), 2.90(4H, s), 7.13(2H, d, J=8.0Hz), 7.45(2H, d, J=8.0Hz).

MS: 582 (M+H)<sup>+</sup>

Step 2

Di-tert-butyl {[ (4-{2-[2-(acetylamino)-5-bromo-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (113 mg) and 4N hydrochloric acid in 1,4-dioxane solution (2 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo*. The residue was washed with ethyl acetate to give N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-bromo-1,3-thiazol-2-yl}acetamide hydrochloride (16.8 mg) as a pale yellow amorphous solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.14(3H, s), 2.82-2.97(4H, m), 7.14(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.40(3H, brs),

9.81 (1H, brs), 12.41 (1H, brs).

MS: 382 (M+H)<sup>+</sup> free

**Production Example 16:** Synthesis of N-[4-(2-{4-  
[(aminooxy)methyl]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide

5 Step 1

[4-(Methoxycarbonyl)benzyl](triphenyl)phosphonium bromide  
(6.06 g) and N,N-dimethylformamide (50 ml) were combined under  
nitrogen atmosphere. Then potassium tert-butoxide (1.66 g) and  
N-(4-formyl-1,3-thiazol-2-yl)acetamide (2.1 g) prepared in a  
10 similar manner according to Step 4 of Production Example 1  
were added to the suspension at 0°C. The reaction mixture was  
stirred at room temperature for 6 hours, poured into ice-  
water, and extracted with ethyl acetate. The organic layer was  
washed with 1N-hydrochloric acid, water and saturated sodium  
15 chloride solution, dried over anhydrous magnesium sulfate, and  
concentrated *in vacuo*. The residue was purified by flash  
column chromatography over silica gel with chloroform /  
methanol (20:1 → 10:1) as an eluent, and triturated with ethyl  
ether to give a mixture of methyl 4-{(Z)-2-[2-(acetylamino)-  
20 1,3-thiazol-4-yl]ethenyl}benzoate and methyl 4-{(E)-2-[2-  
(acetylamino)-1,3-thiazol-4-yl]ethenyl}benzoate (Z : E = 3 :  
1) (4.05 g) as a colorless solid.

mp. 164-165.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.13 (3Hx3/4, s), 2.16 (3Hx1/4, s),  
25 3.85 (3H, s), 6.61 (2Hx3/4, s), 7.05 (1Hx3/4, s), 7.26 (1Hx1/4, d,  
J=15.5Hz), 7.27 (1Hx1/4, s), 7.37 (1Hx1/4, d, J=15.5Hz),  
7.64 (2Hx3/4, d, J=8.5Hz), 7.69 (2Hx1/4, d, J=8.5Hz),  
7.90 (2Hx3/4, d, J=8.5Hz), 7.94 (2Hx1/4, d, J=8.5Hz), 12.05 (1H,  
brs).

30 MS: 303 (M+H)<sup>+</sup>

Step 2

Methyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-  
yl]ethyl}benzoate was prepared in a similar manner according

to Step 2 of Production Example 9.

mp. 170-171°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.86-2.95(2H, m), 2.97-3.05(2H, m), 3.83(3H, s), 6.72(1H, s), 7.35(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 12.08(1H, brs).

MS: 305 (M+H)<sup>+</sup>

### Step 3

To a stirred solution of methyl 4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzoate (1.8 g) in dry tetrahydrofuran (36 ml) was added dropwise 1.0 M diisobutylaluminium hydride solution in toluene (20.7 ml) at -78°C over 15 minutes under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours, and then the reaction was quenched with water (1 ml). The mixture was stirred at room temperature for 30 minutes, dried over anhydrous magnesium sulfate, and filtered through a pad of Celite. The solvent was evaporated in vacuo. The residual solid was washed with ethyl ether to give N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (1.03 g) as a colorless solid.

mp. 162-165°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.80-2.95(4H, m), 4.44(2H, d, J=5.5Hz), 5.09(1H, t, J=5.5Hz), 6.72(1H, s), 7.14(2H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 12.08(1H, brs).

MS: 277 (M+H)<sup>+</sup>

### Step 4

N-(4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (250 mg), 2-hydroxy-1H-isoindole-1,3(2H)-dione (155 mg), triphenylphosphine (249 mg) and tetrahydrofuran (5 ml) were combined under nitrogen atmosphere, and then diethyl azodicarboxylate (0.15 ml) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 6 hours, poured into saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic layer

was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (20:1) as an eluent, and  
5 trituted with ethyl acetate to give N-{4-[2-(4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy)methyl]phenyl)ethyl]-1,3-thiazol-2-yl}acetamide (218.2 mg) as a colorless solid.  
mp. 225-226°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.82-3.00 (4H, m),  
10 5.12 (2H, s), 6.69 (1H, s), 7.23 (2H, d, J=8.0Hz), 7.41 (2H, d, J=8.0Hz), 7.86 (4H, s), 12.08 (1H, brs).

MS: 422 (M+H)<sup>+</sup>

#### Step 5

N-{4-[2-(4-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy)methyl]phenyl)ethyl]-1,3-thiazol-2-yl}  
15 acetamide (200 mg), methylhydrazine (0.038 ml) and dichloromethane (4 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 hours, and filtered *in vacuo*. The filtrate  
20 was washed with saturated sodium hydrogen carbonate solution, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with acetonitrile to give N-[4-(2-{4-[(aminooxy)methyl]phenyl)ethyl)-1,3-thiazol-2-yl]acetamide  
25 (81.8 mg) as a colorless solid.

mp. 130-130.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.82-2.97 (4H, m),  
4.51 (2H, s), 6.01 (2H, s), 6.73 (1H, s), 7.17 (2H, d, J=8.0Hz),  
7.22 (2H, d, J=8.0Hz), 12.09 (1H, brs).

30 MS: 292 (M+H)<sup>+</sup>

Production Example 17: Synthesis of N-{4-[2-(4-[(methyleneamino)oxy)methyl]phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

N-[4-(2-(4-[(Aminooxy)methyl]phenyl)ethyl)-1,3-thiazol-2-yl]acetamide (30 mg) prepared in a similar manner according to Production Example 16, 37% formaldehyde (8  $\mu$ l) and dry methanol (1 ml) were combined under nitrogen atmosphere. The reaction  
5 mixture was stirred at room temperature for 6 hours and concentrated *in vacuo*. The residue was purified by preparative silica gel column chromatography with chloroform / methanol (20:1) as an eluent, and triturated with ethyl ether to give  
N-[4-[2-(4-[(methyleneamino)oxy]methyl]phenyl)ethyl]-1,3-  
10 thiazol-2-yl]acetamide (20.9 mg) as a colorless solid.  
mp. 136.5-137°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>),  $\delta$  (ppm): 2.11 (3H, s), 2.83-2.97 (4H, m),  
5.01 (2H, s), 6.61 (1H, d, J=7.5Hz), 6.73 (1H, s), 7.09 (1H, d,  
J=7.5Hz), 7.18 (2H, d, J=8.0Hz), 7.24 (2H, d, J=8.0Hz),  
15 12.08 (1H, brs).

MS: 304 (M+H)<sup>+</sup>

**Production Example 18:** Synthesis of N-[5-[2-(4-  
[amino(imino)methyl]amino)phenyl)ethyl]-1,3-thiazol-2-  
yl]acetamide hydrochloride

20 Step 1

A solution of 1,1,3,3-tetramethoxypropane (10 g) and hydrochloric acid concentrate (0.43 ml) in water (11 ml) was stirred at room temperature for 10 minutes. Bromine (3.14 ml) was added dropwise to the solution at room temperature over 50  
25 minutes. The reaction mixture was stirred at room temperature for 20 minutes, and concentrated *in vacuo*. The residual solid was washed with water to give 2-bromomalonaldehyde (3.6 g) as a yellow solid.

mp. 147-148°C

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta$  (ppm): 4.73-4.80 (1H, m), 8.47 (2H, brs).

MS: 149 (M-H)<sup>+</sup>

Step 2

N'-((E)-Ethanoyl)carbamimidothioic acid (2.74 g) and

acetone (20 ml) were combined under nitrogen atmosphere. Then 2-bromomalonaldehide (3.5 g) was added to the solution under reflux. The reaction mixture was refluxed for an hour, and cooled to room temperature. The precipitate was filtered *in vacuo*. The solid was washed with water and acetone, and purified by flash column chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give N-(5-formyl-1,3-thiazol-2-yl)acetamide (1.21 g) as an off-white solid.  
mp. 235-235.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.21(3H, s), 8.41(1H, s), 9.95(1H, s), 12.71(1H, brs).

MS: 169(M-H)<sup>+</sup>

### Step 3

N-{5-[(Z)-2-(4-Nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 1.

mp. 221-223°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.07(3H, s), 6.63(1H, d, J=12.0Hz), 6.92(1H, d, J=12.0Hz), 7.55(1H, s), 7.62(2H, d, J=9.0Hz), 8.24(2H, d, J=9.0Hz), 12.16(1H, brs).

MS: 290(M+H)<sup>+</sup>

### Step 4

A mixture of N-{5-[(Z)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (1 g) and 10% palladium carbon (1.04 g) in ethyl acetate (100 ml) and N,N-dimethylformamide (20 ml) was stirred under 4 atm hydrogen at ambient temperature for 4 hours. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (30:1 → 20:1) as an eluent, and triturated with ethyl ether to give N-{5-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (240.9 mg) as an off-white solid.

mp. 218-219.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.70(2H, t, J=7.5Hz), 2.92(2H, t, J=7.5Hz), 4.85(2H, s), 6.47(2H, d, J=8.5Hz), 6.86(2H, d, J=8.5Hz), 7.08(1H, s), 11.86(1H, brs).

<sup>5</sup> MS: 262 (M+H)<sup>+</sup>

#### Step 5

N-{5-[2-(4-Aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (100 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboximidine (119 mg), N,N-dimethylformamide (1 ml) and  
<sup>10</sup> tetrahydrofuran (2 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at 50°C for 5.5 hours. After cooled to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by preparative silica gel column chromatography with n-hexane /  
<sup>15</sup> ethyl acetate (1:2) as an eluent to give di-tert-butyl {[4-{2-[2-(acetylamino)-1,3-thiazol-5-yl]ethyl}phenyl)amino]-methylidene}biscarbamate (93.9 mg) as a colorless solid.  
mp. 203-205°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.40(9H, s), 1.51(9H, s), 2.10(3H, s), 2.87(2H, t, J=7.5Hz), 3.02(2H, t, J=7.5Hz), 7.11(1H, s),  
<sup>20</sup> 7.21(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz), 9.96(1H, brs), 11.43(1H, brs), 11.88(1H, brs).

MS: 504 (M+H)<sup>+</sup>

#### Step 6

<sup>25</sup> The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 105-107°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.91(2H, t, J=7.5Hz), 3.04(2H, t, J=7.5Hz), 7.14(1H, s), 7.14(2H, d, J=8.5Hz),  
<sup>30</sup> 7.32(2H, d, J=8.5Hz), 7.46(3H, brs), 9.89(1H, s), 11.95(1H, brs).

MS: 304 (M+H)<sup>+</sup> free

Production Example 19: Synthesis of N-{4-[2-(4-

{[imino(methylamino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

A mixture of methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydriodide (50 mg)  
5 prepared in a similar manner according to Production Example 4, 40% methylamine in methanol (0.056 ml) and ethanol (1 ml) was stirred at ambient temperature for 20 hours. The precipitated crystals were filtered and washed with ethanol to give N-{4-[2-(4-{[imino(methylamino)methyl]amino}phenyl)-  
10 ethyl]-1,3-thiazol-2-yl}acetamide (18 mg).  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11(3H, s), 2.64(3H, s), 2.83(4H, s), 6.67(2H, d, J=7Hz), 6.73(1H, s), 7.01(2H, d, J=7Hz).  
MS (M+H)=318

**Production Example 20:** Synthesis of N-{4-[2-(4-{[amino(imino)-methyl]amino}phenyl)ethyl]-5-chloro-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

Di-tert-butyl {[4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (150 mg)  
20 prepared in a similar manner according to Step 5 of Production Example 18 was dissolved in methanol (1.5 ml) and tetrahydrofuran (3 ml) under nitrogen atmosphere. Then N-chlorosuccinimide (59.7 mg) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 29  
25 hours, and diluted in ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate solution, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give di-tert-  
30 butyl {[4-{2-[2-(acetylamino)-5-chloro-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (111 mg) as an off-white solid.  
mp. 220-221°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.13(3H, s), 2.81-2.94(4H, m), 7.15(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 9.95(1H, brs), 11.43(1H, brs), 12.38(1H, brs).

MS: 538(M+H)<sup>+</sup>

<sup>5</sup> Step 2

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 82-84°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.14(3H, s), 2.82-2.97(4H, m),  
<sup>10</sup> 7.14(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.42(3H, brs), 9.85(1H, brs), 12.38(1H, brs).

MS: 338(M+H)<sup>+</sup> free

Production Example 21: Synthesis of N-(4-{2-[4-  
({[amino(imino)methyl]amino)methyl]phenyl}ethyl)-1,3-thiazol-  
<sup>15</sup> 2-yl)acetamide hydrochloride

Step 1

A mixture of N-(4-{2-[4-(aminomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (20 mg) prepared in a similar manner according to Production Example 12, N,N'-bis(tert-  
<sup>20</sup> butoxycarbonyl)-1H-pyrazole-1-carboxamide (23 mg) and tetrahydrofuran (0.5 ml) was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica-gel with chloroform as an eluent. The crystalline  
<sup>25</sup> residue was collected and washed with diisopropyl ether to give di-tert-butyl{[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}benzyl)amino]methylenidene}biscarbamate (22 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.47(9H, s), 1.50(9H, s), 2.24(3H, s), 2.87-3.03(4H, m), 6.50(1H, s), 7.13(2H, d, J=7Hz), 7.22(2H, d,  
<sup>30</sup> J=7Hz).

MS (M+H)=518

Step 2

A mixture of di-tert-butyl{[(4-{2-[2-(acetylamino)-1,3-

thiazol-4-yl]ethyl}benzyl)amino]methylidene}biscarbamate (20 mg), dichloromethane (2 drops) and 4N hydrogen chloride in 1,4-dioxane (0.5 ml) was stirred for 15 hours. The precipitated crystals were filtered and washed with 1,4-dioxane to give N-(4-{2-[4-({[amino(imino)methyl]amino}-methyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (13 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12(3H, s), 2.80-3.00(4H, m), 4.32(2H, d, J=7Hz), 6.73(1H, s), 7.20(4H, s), 8.04(1H, t, J=7Hz).

MS (M+H)=318

**Production Example 22:** Synthesis of ethyl 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazole-5-carboxylate hydrochloride

Step 1

Ethyl 4-chloro-3-oxobutanoate (35 g) was dissolved in dichloromethane (70 ml), and then sulfonyl chloride (17.1 ml) in dichloromethane (20 ml) was added dropwise to the solution at 0°C over 15 minutes under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 hours, and concentrated *in vacuo*. The residual oil, N'-((E)-ethanoyl)carbamimidothioic acid (25.1 g) and acetone (600 ml) were combined. The reaction mixture was refluxed for 2.5 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residual solid was washed with water and isopropyl ether to give ethyl 2-(acetylamino)-4-(chloromethyl)-1,3-thiazole-5-carboxylate (21.2 g) as a pale yellow solid.

mp. 164-165°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.30(3H, t, J=7.0Hz), 2.19(3H, s), 4.29(2H, q, J=7.0Hz), 5.00(2H, s), 12.72(1H, s).

MS: 263(M+H)<sup>+</sup>

Step 2: ethyl 2-(acetylamino)-4-[(E)-2-(4-

nitrophenyl)ethenyl]-1,3-thiazole-5-carboxylate

To a stirring solution of ethyl 2-(acetylamino)-4-(chloromethyl)-1,3-thiazole-5-carboxylate (1.0 g, 3.81 mmol) in N,N-dimethylformamide (20 mL) was added triphenylphosphine  
5 (1.2 g, 4.57 mmol) at room temperature. The resultant mixture was stirred at 65°C for 5 hours. To the mixture was added potassium tert-butoxide (555 mg, 4.95 mmol) at 5°C, and the resultant mixture was stirred at 5°C for 30 minutes.  
p-Nitrobenzaldehyde (805 mg, 5.33 mmol) was added at 5°C.  
10 After stirring for 1 hour at room temperature, the reaction was quenched with water, and the mixture was filtered to give the title compound (1.0 g, 72.7%) as a yellow solid.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.40 (3H, t, J=7.2Hz), 2.33 (3H, s), 4.38 (2H, q, J=7.2Hz), 7.59 (1H, d, J=16.0Hz), 7.70 (2H, d, J=8.8Hz), 8.18 (1H, d, J=16.0Hz), 8.22 (2H, d, J=8.8Hz),  
15 8.90 (1H, m).

### Step 3

Ethyl 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylate was prepared in a similar manner  
20 according to Step 6 of Production Example 1.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.35 (3H, t, J=7.0Hz), 2.27 (3H, s), 2.84 (2H, m), 3.28 (2H, m), 3.56 (2H, m), 4.31 (2H, q, J=7.0Hz), 6.61 (2H, d, J=8.3Hz), 7.01 (2H, d, J=8.3Hz), 9.12 (1H, m).

### Step 4

25 Ethyl 2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl}-amino)phenyl]ethyl}-1,3-thiazole-5-carboxylate was prepared in a similar manner according to Step 5 of Production Example 18.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.36 (3H, t, J=7.4Hz), 1.49 (9H, s),  
30 1.53 (9H, s), 2.25 (3H, s), 2.94 (2H, m), 3.34 (2H, m), 4.31 (2H, q, J=7.4Hz), 7.15 (2H, d, J=8.4Hz), 7.41 (2H, d, J=8.4Hz), 9.69 (1H, m), 10.20 (1H, s), 11.63 (1H, s).

### Step 5

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.28(3H, t, J=7.0Hz), 2.18(3H, s), 2.94(2H, m), 3.28(2H, m), 4.23(2H, q, J=7.0Hz), 7.16(2H, d, J=8.4Hz), 7.29(2H, d, J=8.4Hz), 7.37(3H, s), 9.71(1H, s), 12.55(1H, s).

**Production Example 23:** Synthesis of N-{4-[2-(4-[[ (ethylamino) (imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}acetamide

<sup>10</sup> The title compound was prepared in a similar manner according to Production Example 19.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.13(3H, t, J=6Hz), 2.11(3H, s), 2.70-3.00(6H, m), 6.70(1H, s), 6.77(2H, d, J=7Hz), 7.17(2H, d, J=7Hz).

<sup>15</sup> MS (M+H)=332

**Production Example 24:** Synthesis of benzyl 4-[2-(4-[[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-carbamate

Step 1

<sup>20</sup> To an ice-cold mixture of ethyl 2-amino-1,3-thiazole-4-carboxylate (5 g), pyridine (3.36 ml) and dichloromethane (50 ml) was added benzyloxycarbonyl chloride (3.1 ml), and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was washed with saturated aqueous sodium  
<sup>25</sup> hydrogen bicarbonate (30 ml), dried over sodium sulfate and concentrated *in vacuo*. The crystalline residue was collected and washed with diisopropyl ether to give ethyl 2-[[ (benzyloxy) carbonyl]amino]-1,3-thiazole-4-carboxylate (5.1 g).

<sup>30</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.48(3H, t, J=7Hz), 4.38(2H, q, J=7Hz), 5.27(2H, s), 7.36-7.44(5H, m), 7.82(1H, s).

MS (M+H)=307

Step 2

Benzyl 4-(hydroxymethyl)-1,3-thiazol-2-ylcarbamate was prepared in a similar manner according to Step 2 of Production Example 6.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 4.56(2H, s), 5.27(2H, s), 6.80(1H, s),  
5 7.30-7.46(5H, m).

MS (M+H)=265

### Step 3

Benzyl 4-formyl-1,3-thiazol-2-ylcarbamate was prepared in a similar manner according to Step 3 of Production Example 6.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 5.29(2H, s), 7.35-7.45(5H, m),  
7.81(1H, s), 9.80(1H, s).

MS (M+H)=263

### Step 4

Benzyl 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-  
15 ylcarbamate was prepared in a similar manner according to Step  
4 of Production Example 6.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 5.23(2x3/5H, s), 5.25(2x2/5H, s),  
6.56-6.70(1H, m), 7.23(1H, s), 7.30-7.50(5H, m), 7.82(2x2/5H,  
d, J=7Hz), 7.92(2x3/5H, d, J=7Hz), 8.14(2x3/5H, d, J=7Hz),  
20 8.21(2x2/5H, d, J=7Hz).

MS (M+H)=382

### Step 5

A mixture of benzyl 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-  
thiazol-2-ylcarbamate (1.4 g), palladium on carbon (140 mg)  
25 and methanol (2 ml) was stirred under hydrogen atmosphere (4  
atm) at ambient temperature for 8 hours. The catalyst was  
filtered off, and the filtrate was concentrated *in vacuo* to  
give benzyl 4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-  
ylcarbamate (1.2 g).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.77-2.90(4H, m), 5.22(2H, s),  
6.43(1H, s), 6.60(2H, d, J=7Hz); 6.92(2H, d, J=7Hz), 7.32-  
7.40(5H, m).

MS (M+H)=354

Step 6

A mixture of benzyl 4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-ylcarbamate (25 mg), cyanamide (6.0 mg), 4N hydrogen chloride in ethyl acetate (0.018 ml) and ethanol (1 ml) was stirred at 100°C for 72 hours. The reaction mixture was concentrated *in vacuo*. To the residue were added ethyl acetate (5 ml) and saturated aqueous sodium hydrogen bicarbonate (5 ml). The precipitated solid was filtered and washed with ethylacetate and water to give benzyl 4-[2-(4-  
10 { [amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-carbamate (15 mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.63-2.75 (4H, m), 5.07 (2H, s), 6.40 (1H, s), 6.94 (2H, d, J=7Hz), 7.25-7.40 (7H, m).

MS (M+H)=396

15 Production Example 25: Synthesis of N-{4-[2-(4-  
{ [amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl}benzamide hydrochloride

Step 1

Benzyl 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-ylcarbamate (2.7 g) prepared in a similar manner according to Step 4 of Production Example 24 and 6N hydrochloric acid (50 ml) were combined. The reaction mixture was refluxed for 3 hours. After cooled to room temperature, the precipitate was filtered *in vacuo*. The solid was washed with water and  
25 acetonitrile to give 4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-amine (1.34 g) as a yellow solid.

mp. 278-278.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 7.02 (1H, s), 7.33 (2H, s), 7.77 (2H, d, J=8.5Hz), 8.25 (2H, d, J=8.5Hz).

30 MS: 248 (M+H)<sup>+</sup>

Step 2

4-[(E)-2-(4-Nitrophenyl)ethenyl]-1,3-thiazol-2-amine (300 mg) and N,N-dimethylaniline (4 ml) were combined under

nitrogen atmosphere, and then benzoyl chloride (0.31 ml) was added dropwise to the suspension. The reaction mixture was stirred at 110°C for 2 hours. After cooled to room temperature, the mixture was diluted with ethyl acetate. The organic solution was washed with 1N hydrochloric acid, water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give N-{4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}benzamide (298.6 mg) as a yellow solid.

mp. 224.5-225°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 7.40 (1H, d, J=16.0Hz), 7.45 (1H, s), 7.53 (1H, d, J=16.0Hz), 7.56 (2H, t, J=7.0Hz), 7.66 (1H, t, J=7.0Hz), 7.84 (2H, d, J=8.5Hz), 8.13 (2H, d, J=7.0Hz), 8.23 (2H, d, J=8.5Hz), 12.80 (1H, brs).

MS: 352 (M+H)<sup>+</sup>

### Step 3

N-{4-[2-(4-Aminophenyl)ethyl]-1,3-thiazol-2-yl}benzamide was prepared in a similar manner according to Step 2 of Production Example 9.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.82 (4H, s), 3.57 (2H, brs), 6.53 (1H, s), 6.61 (2H, d, J=8.0Hz), 6.92 (2H, d, J=8.0Hz), 7.50 (2H, t, J=7.0Hz), 7.60 (1H, t, J=7.0Hz), 7.93 (2H, d, J=7.0Hz), 10.15 (1H, brs).

MS: 324 (M+H)<sup>+</sup>

### Step 4

Di-tert-butyl {[4-{2-[2-(benzoylamino)-1,3-thiazol-4-yl]ethyl}phenyl]amino}methylidene}biscarbamate was prepared in a similar manner according to Step 5 of Production Example 18.

mp. 143-144°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39 (9H, s), 1.51 (9H, s), 2.95 (4H, s), 6.86 (1H, s), 7.22 (2H, d, J=8.5Hz), 7.44 (2H, d, J=8.5Hz),

7.54 (2H, t, J=7.5Hz), 7.63 (1H, t, J=7.5Hz), 8.10 (2H, d, J=7.5Hz), 9.94 (1H, s), 11.44 (1H, brs), 12.66 (1H, brs).

MS: 566 (M+H)<sup>+</sup>

Step 5

5 The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 229-232°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.91-3.05 (4H, m), 6.88 (1H, s), 7.15 (2H, d, J=8.5Hz), 7.32 (2H, d, J=8.5Hz), 7.44 (3H, brs),  
10 7.54 (2H, t, J=7.5Hz), 7.64 (1H, t, J=7.5Hz), 8.10 (2H, d, J=7.5Hz), 9.88 (1H, s).

MS: 366 (M+H)<sup>+</sup> free

Production Example 26: Synthesis of N-{4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-  
15 (methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide  
hydrochloride

Step 1

4-(Methylsulfanyl)benzaldehyde (31.8 g),  
(acetylamino)acetic acid (24.5 g) and acetic anhydride (35 ml)  
20 were combined, and then sodium acetate (8.57 g) was added to the suspension at room temperature under nitrogen atmosphere. The reaction mixture was refluxed for 3.5 hours. After cooled to room temperature, the mixture was poured into ice-water and ethyl acetate with stirring, and filtered *in vacuo*. The  
25 filtrate was separated. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue and the previously obtained solid were combined, and the mixture was purified by flash column chromatography over silica gel  
30 with chloroform / ethyl acetate (30:1) as an eluent, and triturated with isopropyl ether to give (4Z)-2-methyl-4-(4-(methylsulfanyl)benzylidene)-1,3-oxazol-5(4H)-one (17.8 g) as a brown solid.

mp. 154-155°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.38(3H, s), 2.53(3H, s), 7.19(1H, s), 7.36(2H, d, J=8.5Hz), 8.12(2H, d, J=8.5Hz).

### Step 2

5 (4Z)-2-Methyl-4-(4-(methylsulfanyl)benzylidene)-1,3-oxazol-5(4H)-one (17.5 g), 1,4-dioxane (100 ml) and 4N-hydrochloric acid (27 ml) were combined. The reaction mixture was refluxed for 3 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. Ethyl acetate and water  
10 were added to the residue, and the precipitate was filtered *in vacuo* to give 3-(4-(methylsulfanyl)phenyl)-2-oxopropanoic acid (6.7 g) as a pale brown solid.

mp. 165-167°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.48(3H, s), 6.37(1H, s), 7.23(2H, d, J=8.5Hz), 7.70(2H, d, J=8.5Hz), 9.44(1H, s).

MS: 209(M-H)<sup>+</sup>

### Step 3

3-(4-(Methylsulfanyl)phenyl)-2-oxopropanoic acid (16.2 g), N,N-dimethylformamide (81 ml) and 1,8-  
20 diazabicyclo[5.4.0]undec-7-ene (11.5 ml) were combined at 0°C under nitrogen atmosphere. The mixture was stirred at the same temperature for an hour, and then iodomethane (9.59 ml) was added to the solution at the same temperature. The reaction mixture was stirred at room temperature for 4 hours, poured  
25 into 1N-hydrochloric acid, and extracted with ethyl acetate (twice). The combined organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform  
30 / ethyl acetate (30:1) as an eluent, and triturated with isopropyl ether / n-hexane to give methyl 3-(4-(methylsulfanyl)phenyl)-2-oxopropanoate (8.6 g) as a dark yellow solid.

mp. 112-113°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.48 (3H, s), 3.79 (3H, s), 6.41 (1H, s), 7.24 (2H, d, J=8.5Hz), 7.72 (2H, d, J=8.5Hz), 9.52 (1H, brs).

MS: 223 (M-H)<sup>+</sup>

<sup>5</sup> Step 4

Methyl 3-(4-(methylsulfanyl)phenyl)-2-oxopropanoate (2.84 g), pyridinium tribromide (4.95 g), dichloromethane (140 ml) and acetic acid (0.5 ml) were combined at 0°C under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 2  
<sup>10</sup> hours, and poured into water. The mixture was extracted with ethyl acetate (twice). The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual oil was dissolved in ethanol (55 ml), and then thiourea (1.25 g) was added to the solution. The reaction  
<sup>15</sup> mixture was refluxed for 1 hour under nitrogen atmosphere. After cooled to 0°C, water was added to the solution. The precipitate was filtered *in vacuo* to give methyl 2-amino-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (2.67 g) as a brown solid.

<sup>20</sup> mp. 184-185°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.50 (3H, s), 3.64 (3H, s), 7.25 (2H, d, J=8.5Hz), 7.34 (2H, d, J=8.5Hz).

MS: 281 (M+H)<sup>+</sup>

Step 5

<sup>25</sup> Methyl 2-amino-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (8.8 g) was dissolved in pyridine (88 ml), and then acetyl chloride (6.7 ml) was added dropwise to the solution at 0°C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 minutes and at  
<sup>30</sup> 50°C for 2 hours. After cooled to 0°C, water was added to the solution. The precipitate was filtered *in vacuo*, and the solid was washed with ethyl ether to give methyl 2-(acetylamino)-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (9.3 g) as

an off-white solid.

mp. 253-254.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.52(3H, s), 3.70(3H, s), 7.30(2H, d, J=8.5Hz), 7.44(2H, d, J=8.5Hz).

<sup>5</sup> MS: 323(M+H)<sup>+</sup>

#### Step 6

Methyl 2-(acetylamino)-5-[4-(methylthio)phenyl]-1,3-thiazole-4-carboxylate (200 mg) was dissolved in tetrahydrofuran (2 ml), and then lithium aluminium hydride (35.3 mg) was added portionwise to the solution at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 30 minutes, and quenched with methanol. Ethyl acetate and 1N hydrochloric acid were added to the mixture, and extracted. The aqueous layer was extracted with ethyl acetate (twice). The combined organic layer was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was dissolved in methanol (0.4 ml) and chloroform (7 ml). Then manganase (IV) oxide (1.08 g) was added to the solution under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 13 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give N-{4-formyl-5-[4-(methylthio)phenyl]-1,3-thiazol-2-yl}acetamide (153.6 mg) as a pale brown amorphous substance. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 2.54(3H, s), 7.38(2H, d, J=8.5Hz), 7.58(2H, d, J=8.5Hz), 9.77(1H, s), 12.59(1H, brs).

<sup>30</sup> MS: 293(M+H)<sup>+</sup>

#### Step 7

N-{5-[4-(Methylthio)phenyl]-4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide was prepared

in a similar manner according to Step 1 of Production Example 9.

mp. 228-230°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.19(3H, s), 2.54(3H, s), 7.32(1H, d, J=16.0Hz), 7.40(2H, d, J=8.5Hz), 7.46(1H, d, J=16.0Hz), 7.47(2H, d, J=8.5Hz), 7.79(2H, d, J=9.0Hz), 8.19(2H, d, J=9.0Hz), 12.38(1H, brs).

MS: 412 (M+H)<sup>+</sup>

#### Step 8

Potassium peroxymonosulfate (408 mg) was suspended in water (1 ml) and tetrahydrofuran (1 ml), and then N-{5-[4-(methylthio)phenyl]-4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (182 mg) in tetrahydrofuran (3 ml) was added dropwise to the suspension at 0°C. The reaction mixture was stirred at room temperature for 2 hours, and then water was added to the suspension. The precipitate was filtered in vacuo. The solid was washed with water and ethyl acetate to give N-{5-[4-(methylsulfonyl)phenyl]-4-[(E)-2-(4-nitrophenyl)ethenyl]-1,3-thiazol-2-yl}acetamide (83 mg) as a yellow solid.

mp. 294-295°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.21(3H, s), 3.30(3H, s), 7.40(1H, d, J=16.0Hz), 7.54(1H, d, J=16.0Hz), 7.82(2H, d, J=8.5Hz), 7.84(2H, d, J=8.5Hz), 8.05(2H, d, J=8.5Hz), 8.20(2H, d, J=8.5Hz), 12.51(1H, brs).

MS: 442 (M-H)<sup>+</sup>

#### Step 9

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 2 of Production Example 9.

mp. 202-204°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17(3H, s), 2.77-2.88(4H, m),

3.24(3H, s), 6.84(2H, brs), 6.45(2H, d, J=8.5Hz), 6.77(2H, d, J=8.5Hz), 7.49(2H, d, J=8.5Hz), 7.91(2H, d, J=8.5Hz), 12.34(1H, brs).

MS: 416(M+H)<sup>+</sup>

<sup>5</sup> Step 10

Di-tert-butyl {[4-{2-[2-(acetylamino)-5-(4-(methylsulfonyl)phenyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 5 of Production Example 18.

<sup>10</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.17(3H, s), 2.97(4H, s), 3.24(3H, s), 7.11(2H, d, J=8.5Hz), 7.38(2H, d, J=8.5Hz), 7.56(2H, d, J=8.5Hz), 7.92(2H, d, J=8.5Hz), 9.92(1H, s), 11.43(1H, brs), 12.34(1H, brs).

MS: 658(M+H)<sup>+</sup>

<sup>15</sup> Step 11

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 145-146.5°C

<sup>20</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 2.99(4H, brs), 3.25(3H, s), 7.11(2H, d, J=8.0Hz), 7.22(2H, d, J=8.0Hz), 7.38(3H, brs), 7.57(2H, d, J=8.0Hz), 7.94(2H, d, J=8.0Hz), 9.79(1H, s), 12.36(1H, brs).

MS: 458(M+H)<sup>+</sup> free

Production Example 27: Synthesis of 2-(acetylamino)-4-[2-(4-  
<sup>25</sup> {[amino(imino)methyl]amino}phenyl)ethyl]-N-methyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Ethyl 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylate (310 mg) prepared in a similar manner  
<sup>30</sup> according to Step 3 of Production Example 22 was dissolved in tetrahydrofuran (6 ml) under nitrogen atmosphere. Then di(tert-butyl)dicarbonate (223 mg) in tetrahydrofuran (1 ml) was added to the solution at room temperature. The reaction

mixture was refluxed for 2 hours. After cooled to room temperature, the mixture was concentrated *in vacuo*. The residual solid was washed with ethyl ether to give ethyl 2-(acetylamino)-4-(2-(4-[(tert-butoxycarbonyl)amino]phenyl)-ethyl)-1,3-thiazole-5-carboxylate (370.7 mg) as an off-white solid.

mp. 213-214°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.26(3H, t, J=7.0Hz), 1.46(9H, s), 2.17(3H, s), 2.85(2H, t, J=7.5Hz), 3.23(2H, t, J=7.5Hz), 4.22(2H, q, J=7.0Hz), 7.04(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 9.23(1H, brs), 12.55(1H, brs).

MS: 434 (M+H)<sup>+</sup>

#### Step 2

Ethyl 2-(acetylamino)-4-(2-(4-[(tert-butoxycarbonyl)-amino]phenyl)ethyl)-1,3-thiazole-5-carboxylate (3 g), 1N-aqueous sodium hydroxide solution (17.3 ml) and ethanol (30 ml) were combined, and the mixture was refluxed for 5 hours. After cooled to room temperature, the organic solvent was removed *in vacuo*. The aqueous solution was acidified (pH=4) with 1N-hydrochloric acid, and extracted with ethyl acetate (twice). The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was dissolved in pyridine (45 ml), and then acetyl chloride (1.48 ml) was added dropwise to the solution at 0°C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 13 hours, and pyridine was removed *in vacuo*. Water was added to the residue, and acidified with 1N-hydrochloric acid. The precipitate was collected *in vacuo*. The solid was washed with water and ethyl ether to give 2-(acetylamino)-4-(2-(4-[(tert-butoxycarbonyl)-amino]phenyl)ethyl)-1,3-thiazole-5-carboxylic acid (2.23 g) as an off-white solid.

mp. 237-238°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.85(2H, m), 3.23(2H, m), 7.04(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 9.24(1H, s), 12.46(1H, s).

MS: 404 (M-H)<sup>+</sup>

<sup>5</sup> Step 3

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (80 mg), 30% methylamine in ethanol solution (0.02 ml), 1-hydroxybenzotriazole (29.3 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (39.7 mg) in dichloromethane (1 ml) and N,N-dimethylformamide (0.5 ml) was stirred at ambient temperature for 20 hours. The reaction mixture was poured into saturated sodium hydrogen carbonate solution, and extracted with chloroform. The organic layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give tert-butyl 4-(2-{2-(acetylamino)-5-[(methylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenylcarbamate (92.8 mg) as an off-white amorphous substance.

<sup>20</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.69(3H, d, J=4.5Hz), 2.78-2.86(2H, m), 3.12-3.20(2H, m), 7.06(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.91(1H, q, J=4.5Hz), 9.22(1H, brs), 12.34(1H, brs).

MS: 419 (M+H)<sup>+</sup>

<sup>25</sup> Step 4

tert-Butyl 4-(2-{2-(acetylamino)-5-[(methylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenylcarbamate (95 mg) and trifluoroacetic acid (2 ml) were combined at 0°C. The reaction mixture was stirred at room temperature for an hour, and concentrated *in vacuo*. The residue was dissolved in chloroform. The organic solution was washed with 1N sodium hydroxide solution, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and

concentrated *in vacuo*. The residue was purified by preparative silica gel column chromatography with chloroform / methanol (10:1) as an eluent to give 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-methyl-1,3-thiazole-5-carboxamide (49 mg) as an off-white amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.68(3H, d, J=4.5Hz), 2.67-2.75(2H, m), 3.05-3.15(2H, m), 4.83(2H, brs), 6.47(2H, d, J=8.5Hz), 6.84(2H, d, J=8.5Hz), 7.85(1H, q, J=4.5Hz), 12.33(1H, brs).

MS: 319(M+H)<sup>+</sup>

#### Step 5

Di-tert-butyl {[4-{2-[2-(acetylamino)-5-(methylaminocarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]-methylidene}biscarbamate was prepared in a similar manner according to Step 5 of Production Example 18.

mp. 245-246°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.40(9H, s), 1.51(9H, s), 2.14(3H, s), 2.68(3H, d, J=4.5Hz), 2.85-2.94(2H, m), 3.14-3.25(2H, m), 7.17(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 7.88(1H, q, J=4.5Hz), 9.94(1H, s), 11.44(1H, brs), 12.38(1H, brs).

MS: 561(M+H)<sup>+</sup>

#### Step 6

The title compound was prepared in a similar manner according to Step 2 of Production Example 15.

mp. 101-104°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.67(3H, d, J=4.5Hz), 2.86-2.96(2H, m), 3.16-3.26(2H, m), 7.14(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 7.41(3H, brs), 7.99(1H, q, J=4.5Hz), 9.81(1H, s), 12.36(1H, brs).

MS: 361(M+H)<sup>+</sup> free

**Production Example 28:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-phenyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (80 mg), aniline (0.019 ml), benzotriazole-1-yl-oxy-tris-  
5 pyrrolidino-phosphonium hexafluorophosphate (113 mg) and N,N-diisopropylethylamine (0.076 ml) in N,N-dimethylformamide (2 ml) was stirred at ambient temperature for 21 hours and at 55°C for 3 hours. The reaction mixture was poured into 1N  
hydrochloric acid, and extracted with chloroform. The organic  
10 layer was washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give  
tert-butyl 4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-  
15 thiazol-4-yl]ethyl}phenylcarbamate (57.2 mg) as a colorless solid.

mp. 199-200°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.18(3H, s), 2.81-  
2.91(2H, m), 3.14-3.24(2H, m), 7.05(2H, d, J=8.5Hz), 7.08(1H,  
20 t, J=8.5Hz), 7.26-7.36(4H, m), 7.64(2H, d, J=8.5Hz), 9.22(1H, brs), 9.95(1H, brs), 12.44(1H, brs).

MS: 481 (M+H)<sup>+</sup>

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-phenyl-1,3-  
25 thiazole-5-carboxamide was prepared from tert-butyl 4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenylcarbamate in a similar manner according to Step 4 of Production Example 27.

mp. 104-105°C

30 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 2.71-2.81(2H, m), 3.09-3.18(2H, m), 5.07(2H, brs), 6.48(2H, d, J=8.0Hz), 6.85(2H, d, J=8.0Hz), 7.08(1H, t, J=8.0Hz), 7.33(2H, t, J=8.0Hz), 7.65(2H, d, J=8.0Hz), 9.93(1H, brs), 12.44(1H, brs).

MS: 381 (M+H)<sup>+</sup>

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-phenyl-1,3-thiazole-5-carboxamide in a similar manner according to Step 5 of Production Example 18.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.18(3H, s), 2.87-2.98(2H, m), 3.17-3.29(2H, m), 7.08(1H, t, J=8.0Hz), 7.16(2H, d, J=8.5Hz), 7.31(2H, t, J=8.0Hz), 7.41(2H, d, J=8.5Hz), 7.64(2H, d, J=8.0Hz), 9.93(2H, s), 11.43(1H, brs), 12.46(1H, brs).

MS: 623 (M+H)<sup>+</sup>

Step 4

The title compound was prepared from di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(anilinocarbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate in a similar manner according to Step 6 of Production Example 27.

mp. 152-155°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.19(3H, s), 2.90-3.01(2H, m), 3.17-3.29(2H, m), 7.09(1H, t, J=8.0Hz), 7.13(2H, d, J=8.0Hz), 7.26(2H, d, J=8.0Hz), 7.33(2H, t, J=8.0Hz), 7.40(3H, brs), 7.64(2H, d, J=8.0Hz), 9.79(1H, s), 10.02(1H, s), 12.46(1H, s).

MS: 423 (M+H)<sup>+</sup> free

**Production Example 29:** Synthesis of 2-(acetylamino)-4-[2-(4-[[amino(imino)methyl]amino]phenyl)ethyl]-N,N-dimethyl-1,3-thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl [4-(2-{2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl]ethyl}phenyl]carbamate was prepared from the compound of Step 2 of Production Example 27 in a similar manner according

to Step 3 of Production Example 27.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.14(3H, s), 2.84(4H, s), 2.85(6H, s), 7.01(2H, d, J=8.5Hz), 7.31(2H, d, J=8.5Hz), 9.21(1H, brs), 12.33(1H, brs).

5 MS: 433(M+H)<sup>+</sup>

#### Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N,N-dimethyl-1,3-thiazole-5-carboxamide was prepared from tert-butyl [4-(2-(2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl)ethyl)phenyl]carbamate in a similar manner according to Step 4 of Production Example 27.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.14(3H, s), 2.70-2.77(4H, m), 2.86(6H, s), 4.83(2H, s), 6.45(2H, d, J=8.5Hz), 6.78(2H, d, J=8.5Hz), 12.32(1H, brs).

15 MS: 333(M+H)<sup>+</sup>

#### Step 3

Di-tert-butyl ((Z)-{[4-(2-(2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl)ethyl)phenyl]amino)methylidene)biscarbamate was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N,N-dimethyl-1,3-thiazole-5-carboxamide in a similar manner according to Step 5 of Production Example 18.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.14(3H, s), 2.85(6H, s), 2.89(4H, s), 7.12(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 9.92(1H, s), 11.43(1H, brs), 12.36(1H, brs).

25 MS: 575(M+H)<sup>+</sup>

#### Step 4

The title compound was prepared from di-tert-butyl ((Z)-{[4-(2-(2-(acetylamino)-5-[(dimethylamino)carbonyl]-1,3-thiazol-4-yl)ethyl)phenyl]amino)methylidene)biscarbamate in a similar manner according to Step 6 of Production Example 27.

mp. 78-80°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.81-2.96(4H, m),

2.88 (6H, s), 7.11 (2H, d, J=8.5Hz), 7.18 (2H, d, J=8.5Hz),  
7.38 (3H, brs), 9.77 (1H, s), 12.34 (1H, s).

MS: 375 (M+H)<sup>+</sup> free

**Production Example 30:** Synthesis of 2-(acetylamino)-4-[2-(4-  
5 { [amino(imino)methyl]amino}phenyl)ethyl]-N-benzyl-1,3-  
thiazole-5-carboxamide hydrochloride

Step 1

tert-Butyl [4-(2-{2-(acetylamino)-5-  
[(benzylamino)carbonyl]-1,3-thiazol-4-  
10 yl}ethyl)phenyl]carbamate was prepared from the compound of  
Step 2 of Production Example 27 in a similar manner according  
to Step 3 of Production Example 27.

mp. 184-185°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46 (9H, s), 2.15 (3H, s), 2.79-  
15 2.87 (2H, m), 3.12-3.22 (2H, m), 4.37 (2H, d, J=6.5Hz), 7.02 (2H,  
d, J=8.5Hz), 7.18-7.36 (7H, m), 8.56 (1H, t, J=6.5Hz), 9.22 (1H,  
brs), 12.37 (1H, brs).

MS: 495 (M+H)<sup>+</sup>

Step 2

20 2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-benzyl-1,3-  
thiazole-5-carboxamide was prepared from tert-butyl [4-(2-{2-  
(acetylamino)-5-[(benzylamino)carbonyl]-1,3-thiazol-4-  
yl}ethyl)phenyl]carbamate in a similar manner according to  
Step 4 of Production Example 27.

25 mp. 200-201°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15 (3H, s), 2.66-2.76 (2H, m), 3.07-  
3.15 (2H, m), 4.38 (2H, d, J=6.0Hz), 4.83 (2H, s), 6.46 (2H, d,  
J=8.5Hz), 6.81 (2H, d, J=8.5Hz), 7.20-7.36 (5H, m), 8.52 (1H, t,  
J=6.0Hz), 12.32 (1H, brs).

30 MS: 395 (M+H)<sup>+</sup>

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-  
[(benzylamino)carbonyl]-1,3-thiazol-4-

yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-benzyl-1,3-thiazole-5-carboxamide in a similar manner according to Step 5 of Production Example 18.

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.85-2.94(2H, m), 3.16-3.25(2H, m), 4.37(2H, d, J=6.0Hz), 7.12(2H, d, J=8.5Hz), 7.22-7.36(5H, m), 7.40(2H, d, J=8.5Hz), 8.32(1H, s), 8.54(1H, t, J=6.0Hz), 9.94(1H, brs), 11.44(1H, brs).

<sup>10</sup> MS: 637 (M+H)<sup>+</sup>

#### Step 4

The title compound was prepared from di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(benzylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino)methylidene)biscarbamate in a similar  
<sup>15</sup> manner according to Step 6 of Production Example 27.

mp. 128-130°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17(3H, s), 2.85-2.96(2H, m), 3.16-3.27(2H, m), 4.36(2H, d, J=6.0Hz), 7.12(2H, d, J=8.5Hz), 7.17-7.35(7H, m), 7.40(3H, brs), 8.66(1H, t, J=6.0Hz), 9.78(1H, s), 12.38(1H, s).

<sup>20</sup> MS: 437 (M+H)<sup>+</sup> free

**Production Example 31:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide hydrochloride

#### <sup>25</sup> Step 1

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid (100 mg), (4-nitrobenzyl)amine hydrochloride (46.5 mg), 1-hydroxybenzotriazole (36.7 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (40.2 mg) in DMF (2 ml) was  
<sup>30</sup> stirred at ambient temperature for 73 hours. The reaction mixture was poured into saturated NaHCO<sub>3</sub>, and extracted with CHCl<sub>3</sub>. The organic layer was washed with water and brine,

dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo* to give tert-butyl{4-[2-(2-(acetylamino)-5-[(4-nitrobenzyl)amino]carbonyl)-1,3-thiazol-4-yl)ethyl]phenyl}carbamate (123.7 mg) as a pale yellow solid.  
5 mp. 204-205°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 1.46(9H, s), 2.16(3H, s), 2.77-2.91(2H, m), 3.12-3.27(2H, m), 4.49(2H, d,  $J=5.5\text{Hz}$ ), 7.01(2H, d,  $J=8.5\text{Hz}$ ), 7.32(2H, d,  $J=8.5\text{Hz}$ ), 7.52(2H, d,  $J=8.5\text{Hz}$ ), 8.21(2H, d,  $J=8.5\text{Hz}$ ), 8.68(1H, t,  $J=5.5\text{Hz}$ ), 9.21(1H, s),  
10 12.40(1H, s).

MS: 540 ( $\text{M}+\text{H}$ ) $^+$

### Step 2

tert-Butyl {4-[2-(2-(acetylamino)-5-[(4-nitrobenzyl)amino]carbonyl)-1,3-thiazol-4-yl)ethyl]phenyl}carbamate (135 mg) and TFA (2 ml) were  
15 combined at 0°C. The reaction mixture was stirred at room temperature for an hour, and concentrated *in vacuo*. The residue was dissolved in MeOH and  $\text{CHCl}_3$ , and made basic (pH=8) by 1N-NaOH. The mixture was concentrated *in vacuo*. The  
20 residual solid was washed with water to give 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide (92.5 mg) as a pale yellow solid.  
mp. 120-121°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.16(3H, s), 2.65-2.81(2H, m), 3.04-  
25 3.21(2H, m), 4.49(2H, d,  $J=5.5\text{Hz}$ ), 5.65(2H, brs), 6.54(2H, d,  $J=8.0\text{Hz}$ ), 6.86(2H, d,  $J=8.0\text{Hz}$ ), 7.54(2H, d,  $J=8.5\text{Hz}$ ), 8.21(2H, d,  $J=8.5\text{Hz}$ ), 8.67(1H, t,  $J=5.5\text{Hz}$ ), 12.39(1H, s).

MS: 440 ( $\text{M}+\text{H}$ ) $^+$

### Step 3

30 2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide (83 mg),  $\text{N,N'}$ -bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboximidine (58.6 mg) and THF (1 ml) were combined under  $\text{N}_2$  atmosphere. The reaction

mixture was stirred at r.t. for 2 hours, and concentrated *in vacuo*. The residual solid was washed with AcOEt to give di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{{(4-nitrobenzyl)amino}carbonyl}}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate (95.4 mg) as an off-white solid.

mp. 251-253°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.38 (9H, s), 1.51 (9H, s), 2.16 (3H, s), 2.81-2.98 (2H, m), 3.16-3.29 (2H, m), 4.49 (2H, d, J=5.5Hz), 7.12 (2H, d, J=8.0Hz), 7.40 (2H, d, J=8.0Hz), 7.53 (2H, d, J=8.5Hz), 8.20 (2H, d, J=8.5Hz), 8.67 (1H, t, J=5.5Hz), 9.93 (1H, s), 11.44 (1H, s), 12.42 (1H, s).

MS: 682 (M+H)<sup>+</sup>

#### Step 4

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{{(4-nitrobenzyl)amino}carbonyl}}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate (70 mg) and 4N HCl in 1,4-dioxane solution (1.5 ml) were combined under N<sub>2</sub> atmosphere. The reaction mixture was stirred at r.t. for 14 hours. The solvent was removed *in vacuo*. The residue was washed with AcOEt to give 2-(acetylamino)-4-[2-(4-{{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-nitrobenzyl)-1,3-thiazole-5-carboxamide hydrochloride (63.7 mg) as a pale green solid.

mp. 138-140°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17 (3H, s), 2.81-3.00 (2H, m), 3.17-3.30 (2H, m), 4.48 (2H, d, J=5.5Hz), 7.12 (2H, d, J=8.0Hz), 7.25 (2H, d, J=8.0Hz), 7.40 (3H, s), 7.55 (2H, d, J=8.0Hz), 8.21 (2H, d, J=8.0Hz), 8.80 (1H, t, J=5.5Hz), 9.81 (1H, s), 12.42 (1H, s).

MS: 482 (M+H)<sup>+</sup> free

**Production Example 32:** Synthesis of 2-(acetylamino)-4-[2-(4-{{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-

(methylsulfonyl)benzyl]-1,3-thiazole-5-carboxamide  
hydrochloride

Step 1

A mixture of 2-(acetylamino)-4-(2-{4-[(tert-  
5 butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic  
acid (120 mg), [4-(methylthio)benzyl]amine (45.4 mg), 1-  
hydroxybenzotriazole (44 mg) and 1-ethyl-3-(3-  
dimethylaminopropyl)carbodiimide hydrochloride (59.6 mg) in  
DMF (2 ml) was stirred at r.t. for 17 hours. The reaction  
10 mixture was poured into saturated NaHCO<sub>3</sub>, and extracted with  
CHCl<sub>3</sub>. The organic layer was washed with water and brine,  
dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The  
residue was purified by preparative silica gel chromatography  
with CHCl<sub>3</sub> / AcOEt (1:1) as an eluent to give tert-butyl 4-{2-  
15 [2-(acetylamino)-5-({[4-(methylthio)benzyl]amino}carbonyl)-  
1,3-thiazol-4-yl]ethyl}phenyl)carbamate (163.5 mg) as an off-  
white solid.

mp. 182-183°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.45(3H,  
20 s), 2.77-2.91(2H, m), 3.09-3.24(2H, m), 4.32(2H, d, J=5.5Hz),  
7.02(2H, d, J=8.5Hz), 7.22(4H, s), 7.33(2H, d, J=8.5Hz),  
8.54(1H, t, J=5.5Hz), 9.22(1H, s), 12.36(1H, s).

MS: 541 (M+H)<sup>+</sup>

Step 2

25 Potassium peroxydisulfate (264 mg) was suspended in  
water (1 ml) and THF (1 ml), and then tert-butyl 4-{2-[2-  
(acetylamino)-5-({[4-(methylthio)benzyl]amino}carbonyl)-1,3-  
thiazol-4-yl]ethyl}phenyl)carbamate (155 mg) in THF (2 ml) was  
added dropwise to the suspension at 0°C. The reaction mixture  
30 was stirred at r.t. for an hour, and then water was added to  
the suspension. The solution was extracted with AcOEt (twice).  
The combined organic layer was washed with brine, dried over  
anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo* to give tert-butyl

(4-{2-[2-(acetylamino)-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate (140.6 mg) as an off-white solid.  
mp. 192.5-193°C

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.73-2.90(2H, m), 3.11-3.27(2H, m), 3.18(3H, s), 4.47(2H, d, J=5.5Hz), 7.03(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.89(2H, d, J=8.5Hz), 8.68(1H, t, J=5.5Hz), 9.22(1H, s), 12.39(1H, s).

<sup>10</sup> MS: 573 (M+H)<sup>+</sup>

### Step 3

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[4-(methylsulfonyl)benzyl]-1,3-thiazole-5-carboxamide was prepared in a similar manner according to Step 2 of Production  
<sup>15</sup> Example 31.

mp. 78-80°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.65-2.80(2H, m), 3.04-3.22(2H, m), 3.19(3H, s), 4.46(2H, d, J=5.5Hz), 4.82(2H, s), 6.46(2H, d, J=8.0Hz), 6.81(2H, d, J=8.0Hz), 7.53(2H, d, J=8.0Hz), 7.89(2H, d, J=8.0Hz), 8.63(1H, t, J=5.5Hz),  
<sup>20</sup> 12.39(1H, s).

MS: 473 (M+H)<sup>+</sup>

### Step 4

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.16(3H, s), 2.81-2.98(2H, m), 3.18(3H, s), 3.18-3.29(2H, m), 4.46(2H, d, J=5.5Hz), 7.14(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz),  
<sup>30</sup> 7.54(2H, d, J=8.5Hz), 7.88(2H, d, J=8.5Hz), 8.67(1H, t, J=5.5Hz), 9.94(1H, s), 11.44(1H, s), 12.41(1H, s).

MS: 715 (M+H)<sup>+</sup>

Step 5

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 94-96°C

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17(3H, s), 2.85-2.99(2H, m), 3.19(3H, s), 3.19-3.30(2H, m), 4.46(2H, d, J=5.5Hz), 7.13(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.40(3H, s), 7.54(2H, d, J=8.5Hz), 7.89(2H, d, J=8.5Hz), 8.78(1H, t, J=5.5Hz), 9.80(1H, s), 12.41(1H, s).

<sup>10</sup> MS: 515 (M+H)<sup>+</sup> free

**Production Example 33:** Synthesis of 2-(acetylamino)-4-[2-(4-([amino(imino)methyl]amino)phenyl)ethyl]-N-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide hydrochloride

<sup>15</sup> Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[4-(trifluoromethyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-  
<sup>20</sup> 5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.16(3H, s), 2.73-2.92(2H, m), 3.12-3.25(2H, m), 4.45(2H, d, J=5.5Hz), 7.01(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.47(2H, d, J=8.5Hz),  
<sup>25</sup> 7.69(2H, d, J=8.5Hz), 8.64(1H, t, J=5.5Hz), 9.22(1H, s), 12.39(1H, s).

MS: 563 (M+H)<sup>+</sup>

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide was  
<sup>30</sup> prepared in a similar manner according to Step 2 of Production Example 31.

mp. 199-201°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10 (3H, s), 2.63-2.78 (2H, m), 3.02-3.18 (2H, m), 4.44 (2H, d, J=5.5Hz), 4.81 (2H, s), 6.46 (2H, d, J=8.0Hz), 6.81 (2H, d, J=8.0Hz), 7.49 (2H, d, J=8.0Hz), 7.69 (2H, d, J=8.0Hz), 8.44 (1H, t, J=5.5Hz), 12.39 (1H, s).

5 MS: 463 (M+H)<sup>+</sup>

### Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(trifluoromethyl)benzyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in  
10 a similar manner according to Step 3 of Production Example 31.  
mp. 188-190°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39 (9H, s), 1.51 (9H, s), 2.16 (3H, s), 2.83-2.97 (2H, m), 3.17-3.29 (2H, m), 4.44 (2H, d, J=5.5Hz), 7.12 (2H, d, J=8.5Hz), 7.40 (2H, d, J=8.5Hz), 7.48 (2H, d,  
15 J=8.0Hz), 7.69 (2H, d, J=8.0Hz), 8.63 (1H, t, J=5.5Hz), 9.94 (1H, s), 11.44 (1H, s), 12.40 (1H, s).

MS: 705 (M+H)<sup>+</sup>

### Step 4

The title compound was prepared in a similar manner  
20 according to Step 4 of Production Example 31.  
mp. 156-158°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17 (3H, s), 2.82-2.99 (2H, m), 3.18-3.31 (2H, m), 4.44 (2H, d, J=5.5Hz), 7.12 (2H, d, J=8.0Hz), 7.25 (2H, d, J=8.0Hz), 7.40 (3H, s), 7.51 (2H, d, J=8.0Hz),  
25 7.71 (2H, d, J=8.0Hz), 8.76 (1H, t, J=5.5Hz), 9.81 (1H, s), 12.41 (1H, s).

MS: 505 (M+H)<sup>+</sup> free

**Production Example 34:** Synthesis of 2-(acetylamino)-4-[2-(4-  
30 {[amino(imino)methyl]amino}phenyl)ethyl]-N-(3-pyridinyl)-1,3-  
thiazole-5-carboxamide dihydrochloride

### Step 1

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-  
5-carboxylic acid was prepared from 2-(acetylamino)-4-(2-{4-

[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 2 of Production Example 31.

mp. 211.5-212°C

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.67-2.80(2H, m), 3.09-3.23(2H, m), 6.51(2H, d, J=8.0Hz), 6.85(2H, d, J=8.0Hz), 12.44(1H, brs).

MS: 306(M+H)<sup>+</sup>

#### Step 2

<sup>10</sup> 2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxylic acid (106 mg) was suspended in THF (2 ml) under N<sub>2</sub> atmosphere. Bis(trimethylsilyl)acetamide (0.253 ml) was added to the suspension at r.t., and the mixture was stirred at r.t. for 15 minutes. Then, N,N'-bis(tert-butoxycarbonyl)-1H-  
<sup>15</sup> pyrazole-1-carboxamide (119 mg) was added to the solution at r.t. The reaction mixture was stirred at r.t. for 20 hours, and concentrated *in vacuo*. The residue was dissolved in CHCl<sub>3</sub>. The organic solution was washed with 1N-HCl, water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The  
<sup>20</sup> residual solid was washed with ethyl ether to give 2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino](tert-butoxycarbonyl)iminomethyl)amino]phenyl}ethyl}-1,3-thiazole-5-carboxylic acid (115.8 mg) as a pale brown solid.

mp. 221.5-223°C

<sup>25</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.44(18H, brs), 2.16(3H, s), 2.91(2H, t, J=7.0Hz), 3.26(2H, t, J=7.0Hz), 7.17(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 9.95(1H, brs), 11.43(1H, brs), 12.48(1H, s).

MS: 548(M+H)<sup>+</sup>

#### <sup>30</sup> Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(3-pyridinylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in

a similar manner according to Step 1 of Production Example 32.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.19(3H, s), 2.87-3.00(2H, m), 3.19-3.32(2H, m), 7.16(2H, d, J=8.5Hz), 7.35(1H, dd, J=8.5, 4.5Hz), 7.41(2H, d, J=8.5Hz), 8.07(1H, m),  
5 8.28(1H, dd, J=4.5, 1.5Hz), 8.81(1H, d, J=1.5Hz), 9.93(1H, s), 10.11(1H, s), 11.43(1H, s), 12.51(1H, s).

MS: 624 (M+H)<sup>+</sup>

#### Step 4

The title compound was prepared in a similar manner  
10 according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.21(3H, s), 2.84-3.07(2H, m), 3.19-3.39(2H, m), 7.13(2H, d, J=7.5Hz), 7.28(2H, d, J=7.5Hz), 7.45(3H, brs), 7.37-8.81(4H, m), 9.93(1H, s), 10.75(1H, s), 12.61(1H, s).

15 MS: 424 (M+H)<sup>+</sup> free

**Production Example 35:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-phenoxybenzyl)-1,3-thiazole-5-carboxamide hydrochloride

#### Step 1

20 Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{{(4-phenoxybenzyl)amino}carbonyl)-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example  
25 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.38(9H, s), 1.51(9H, s), 2.15(3H, s), 2.81-2.97(2H, m), 3.13-3.28(2H, m), 4.35(2H, d, J=5.5Hz), 6.97(4H, d, J=8.5Hz), 7.11(1H, t, J=8.5Hz), 7.13(2H, d, J=8.5Hz), 7.29-7.41(6H, m), 8.54(1H, t, J=5.5Hz), 9.93(1H, s),  
30 11.44(1H, brs), 12.37(1H, brs).

MS: 729 (M+H)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17 (3H, s), 2.81-3.00 (2H, m), 3.13-3.30 (2H, m), 4.35 (2H, d, J=5.5Hz), 6.98 (4H, d, J=8.5Hz), 7.12 (2H, d, J=8.5Hz), 7.13 (1H, t, J=8.5Hz), 7.25 (2H, d, J=8.5Hz), 7.32 (2H, d, J=8.5Hz), 7.40 (2H, t, J=8.5Hz), 7.46 (3H, brs), 8.67 (1H, t, J=5.5Hz), 9.92 (1H, s), 12.39 (1H, brs).

MS: 529 (M+H)<sup>+</sup> free

**Production Example 36:** Synthesis of ethyl 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-1-piperazinecarboxylate

Step 1

Ethyl 4-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)carbonyl]-1-piperazinecarboxylate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.17 (3H, t, J=7.0Hz), 1.39 (9H, brs), 1.50 (9H, brs), 2.15 (3H, s), 2.90 (4H, m), 3.38 (8H, brs), 4.03 (2H, q, J=7.0Hz), 7.12 (2H, d, J=8.5Hz), 7.41 (2H, d, J=8.5Hz), 9.94 (1H, s), 11.46 (1H, brs), 12.40 (1H, brs).

MS: 688 (M+H)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner according to Step 2 of the following Production Example 48.  
mp. 180-182.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.18 (3H, t, J=7.0Hz), 2.07 (3H, s), 2.77 (4H, s), 3.43 (8H, brs), 4.05 (2H, q, J=7.0Hz), 6.89 (2H, d, J=7.5Hz), 7.02 (2H, d, J=7.5Hz).

MS: 488 (M+H)<sup>+</sup>

**Production Example 37:** Synthesis of N-{5-[(4-acetyl-1-piperazinyl)carbonyl]-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-

yl}acetamide

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(4-acetyl-  
1-piperazinyl)carbonyl]-1,3-thiazol-4-

5 yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, brs), 1.50(9H, brs),  
10 1.98(3H, s), 2.15(3H, s), 2.90(4H, m), 3.40(8H, brs), 7.13(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.93(1H, s), 11.43(1H, brs), 12.40(1H, brs).

MS: 658 (M+H)<sup>+</sup>

Step 2

15 The title compound was prepared in a similar manner according to Step 2 of the following Production Example 48.  
mp. 206-207.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.01(3H, s), 2.05(3H, s), 2.73(4H, s), 3.42(8H, brs), 6.77-7.08(4H, m).

20 MS: 458 (M+H)<sup>+</sup>

**Production Example 38:** Synthesis of N-(4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-  
(methylsulfonyl)-1-piperazinyl]carbonyl}-1,3-thiazol-2-  
yl)acetamide hydrochloride

25 Step 1

Di-tert-butyl [(Z)-{[4-[2-(2-(acetylamino)-5-{[4-  
(methylsulfonyl)-1-piperazinyl]carbonyl]-1,3-thiazol-4-  
yl)ethyl]phenyl]amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34  
30 in a similar manner according to Step 1 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.89(3H, s), 2.82-2.96(4H, m), 3.01-3.13(4H, m), 3.44-

3.59(4H, m), 7.14(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz),  
9.94(1H, s), 11.44(1H, brs), 12.40(1H, brs).

MS: 694 (M+H)<sup>+</sup>

#### Step 2

5 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 118-119°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.90(3H, s), 2.83-  
2.98(4H, m), 3.06-3.18(4H, m), 3.50-3.61(4H, m), 7.12(2H, d,  
10 J=8.5Hz), 7.21(2H, d, J=8.5Hz), 7.43(3H, s), 9.90(1H, s),  
12.41(1H, s).

MS: 494 (M+H)<sup>+</sup> free

**Production Example 39:** Synthesis of N-[4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-5-(4-  
15 thiomorpholinylcarbonyl)-1,3-thiazol-2-yl]acetamide  
hydrochloride

#### Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(4-  
thiomorpholinylcarbonyl)-1,3-thiazol-4-  
20 yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
from the compound obtained in Step 2 of Production Example 34  
in a similar manner according to Step 1 of Production Example  
32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H,  
25 s), 2.45-2.61(4H, m), 2.79-2.99(4H, m), 3.55-3.70(4H, m),  
7.13(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.92(1H, s),  
11.44(1H, brs), 12.38(1H, brs).

#### Step 2

The title compound was prepared in a similar manner  
30 according to Step 4 of Production Example 31.

mp. 134-135.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.47-2.62(4H, m), 2.80-  
3.00(4H, m), 3.59-3.73(4H, m), 7.12(2H, d, J=8.5Hz), 7.20(2H,

d, J=8.5Hz), 7.39(3H, s), 9.80(1H, s), 12.38(1H, s).

MS: 433(M+H)<sup>+</sup> free

**Production Example 40:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(1,1-dioxido-4-thiomorpholinyl)carbonyl]-1,3-thiazol-2-yl}acetamide  
hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(1,1-dioxido-4-thiomorpholinyl)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Step 1 of Production Example 39 in a similar manner according to Step 2 of Production Example 32.

mp. 270-271.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.85-2.96(4H, m), 3.09-3.21(4H, m), 3.69-3.83(4H, m), 7.13(2H, d, J=8.5Hz), 7.40(2H, d, J=8.5Hz), 9.93(1H, s), 11.47(1H, brs), 12.42(1H, brs).

MS: 665(M+H)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 185-186°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.92(4H, s), 3.11-3.28(4H, m), 3.76-3.91(4H, m), 7.12(2H, d, J=8.5Hz), 7.22(2H, d, J=8.5Hz), 7.40(3H, s), 9.84(1H, s), 12.40(1H, s).

MS: 465(M+H)<sup>+</sup> free

**Production Example 41:** Synthesis of ethyl 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}carbonyl)-4-piperidinecarboxylate hydrochloride

Step 1

Ethyl 1-{{2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-

butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl]carbonyl}-4-piperidinecarboxylate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.17(3H, t, J=7.0Hz), 1.32-1.56(2H, m), 1.39(9H, s), 1.50(9H, s), 1.73-1.89(2H, m), 2.15(3H, s), 2.44-2.64(1H, m), 2.80-3.01(6H, m), 3.74-3.93(2H, m), 4.06(2H, q, J=7.0Hz), 7.11(2H, d, J=8.5Hz), 7.41(2H, d, J=8.5Hz), 9.93(1H, s), 11.45(1H, brs), 12.36(1H, brs).

MS: 687(M+H)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.18(3H, t, J=7.0Hz), 1.29-1.54(2H, m), 1.73-1.93(2H, m), 2.15(3H, s), 2.44-2.71(1H, m), 2.79-3.09(6H, m), 3.79-3.96(2H, m), 4.09(2H, q, J=7.0Hz), 7.11(2H, d, J=8.5Hz), 7.19(2H, d, J=8.5Hz), 7.40(3H, s), 9.83(1H, s), 12.37(1H, s).

MS: 487(M+H)<sup>+</sup> free

**Production Example 42:** Synthesis of 1-((2-(acetylamino)-4-[2-(4-{[amino(imino)methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl]carbonyl)-4-piperidinecarboxamide hydrochloride

#### Step 1

Ethyl 1-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)carbonyl]-4-piperidinecarboxylate (277.9 mg), 1N-NaOH (1.01 ml) and 1,4-dioxane (3 ml) were combined at 0°C, and the reaction mixture was stirred at r.t. for 3 hours. The mixture was neutralized with 1N-HCl, and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in*

vacuo to give 1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)carbonyl]-4-piperidinecarboxylic acid (262.4 mg) as a pale  
5 yellow amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.28-1.59 (2H, m), 1.45 (18H, s), 1.72-1.90 (2H, m), 2.15 (3H, s), 2.40-2.59 (1H, m), 2.78-3.03 (6H, m), 3.77-3.94 (2H, m), 7.12 (2H, d, J=8.5Hz), 7.40 (2H, d, J=8.5Hz), 9.94 (1H, brs), 11.44 (1H, brs), 12.36 (1H, s).

10 MS: 659 (M+H)<sup>+</sup>

### Step 2

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(aminocarbonyl)-1-piperidiny]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in  
15 a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.29-1.55 (2H, m), 1.39 (9H, s), 1.50 (9H, s), 1.62-1.79 (2H, m), 2.14 (3H, s), 2.22-2.43 (1H, m), 2.78-2.99 (6H, m), 3.89-4.07 (2H, m), 6.80 (1H, s), 7.14 (2H, d, J=8.5Hz), 7.27 (1H, s), 7.41 (2H, d, J=8.5Hz), 9.93 (1H, s),  
20 11.44 (1H, brs), 12.36 (1H, s).

MS: 658 (M+H)<sup>+</sup>

### Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

25 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.27-1.52 (2H, m), 1.64-1.79 (2H, m), 2.15 (3H, s), 2.25-2.44 (2H, m), 2.76-3.02 (6H, m), 6.82 (1H, br), 7.11 (2H, d, J=8.5 Hz), 7.19 (2H, d, J=8.5 Hz), 7.34 (1H, br), 7.41 (4H, s), 9.83 (1H, s), 12.36 (1H, s).

MS: 458 (M+H)<sup>+</sup> free

30 Production Example 43: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)carbonyl)-N-methyl-4-piperidinecarboxamide hydrochloride

### Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-  
[(methylamino) carbonyl]-1-piperidinyl} carbonyl)-1,3-thiazol-4-  
yl]ethyl}phenyl) amino]methylidene}biscarbamate was prepared  
from the compound obtained in Step 1 of Production Example 42  
5 in a similar manner according to Step 1 of Production Example  
32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.30-1.75 (4H, m), 1.39 (9H, s),  
1.50 (9H, s), 2.14 (3H, s), 2.22-2.42 (1H, m), 2.55 (2H, d,  
J=4.5Hz), 2.78-2.99 (6H, m), 3.90-4.03 (2H, m), 7.14 (2H, d,  
10 J=8.5Hz), 7.41 (2H, d, J=8.5Hz), 7.73 (1H, q, J=4.5Hz), 9.93 (1H,  
s), 11.43 (1H, brs), 12.36 (1H, brs).

MS: 672 (M+H)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner  
15 according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.29-1.52 (2H, m), 1.60-  
1.77 (2H, m), 2.15 (3H, s), 2.55 (3H, d, J=4.5 Hz), 2.78-2.98 (6H,  
m), 3.88-4.06 (3H, m), 7.11 (2H, d, J=8.5 Hz), 7.19 (2H, d, J=8.5  
Hz), 7.37 (4H, br), 7.81 (1H, m), 9.75 (1H, s), 12.36 (1H, s).

20 MS: 472 (M+H)<sup>+</sup> free

**Production Example 44:** Synthesis of 1-({2-(acetylamino)-4-[2-  
(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-  
yl}carbonyl)-N,N-dimethyl-4-piperidinecarboxamide  
hydrochloride

#### 25 Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-  
[(dimethylamino) carbonyl]-1-piperidinyl} carbonyl)-1,3-thiazol-  
4-yl]ethyl}phenyl) amino]methylidene}biscarbamate was prepared  
from the compound obtained in Step 1 of Production Example 42  
30 in a similar manner according to Step 1 of Production Example  
32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.30-1.70 (4H, m), 1.39 (9H, s),  
1.50 (9H, s), 2.15 (3H, s), 2.80 (3H, s), 2.79-3.01 (7H, m),

3.00 (3H, s), 3.88-4.06 (2H, m), 7.13 (2H, d, J=8.5Hz), 7.41 (2H, d, J=8.5Hz), 9.92 (1H, s), 11.42 (1H, brs), 12.36 (1H, brs).

MS: 686 (M+H)<sup>+</sup>

### Step 2

5 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.27-1.51 (2H, m), 1.55-1.72 (2H, m), 2.15 (3H, s), 2.80 (3H, s), 2.81-3.00 (6H, m), 3.03 (3H, s), 3.89-3.96 (3H, m), 7.11 (2H, d, J=8.5 Hz), 7.20 (2H, d, J=8.5 Hz), 7.37 (4H, br), 9.79 (1H, s), 12.36 (1H, s).

MS: 486 (M+H)<sup>+</sup>

Production Example 45: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-phenyl-1,3-thiazol-2-yl}acetamide hydrochloride

### 15 Step 1

2-Oxo-3-phenylpropanoic acid (20 g), DMF (100 ml) and DBU (18.2 ml) were combined at 0°C under N<sub>2</sub> atmosphere, and the mixture was stirred at 0°C for an hour. Then iodomethane (15.2 ml) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 3 hours, and poured into 1N-HCl. The mixture was extracted with AcOEt (twice). The combined organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with CHCl<sub>3</sub> / AcOEt (30:1) as an eluent, and triturated with IPE / n-Hexane to give methyl 2-oxo-3-phenylpropanoate (11.2 g) as a pale yellow wax.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 3.92 (3H, s), 6.42 (1H, s), 6.53 (1H, s), 7.28-7.42 (3H, m), 7.77 (2H, dd, J=8.5, 1.5Hz).

MS: 179 (M+H)<sup>+</sup>

### 30 Step 2

Methyl 2-oxo-3-phenylpropanoate (11 g), pyridinium tribromide (24.1 g), CH<sub>2</sub>Cl<sub>2</sub> (490 ml) and AcOH (1.5 ml) were combined at 0°C under N<sub>2</sub> atmosphere. The reaction mixture was

stirred at 0°C for 1.5 hours, poured into water and participated. The organic layer was dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residual oil was dissolved in EtOH (190 ml), and then thiourea (6.11 g) was  
5 added to the solution. The reaction mixture was refluxed for an hour under  $\text{N}_2$  atmosphere. After cooled to 0°C, water was added to the solution. The precipitate was filtered *in vacuo* to give methyl 2-amino-5-phenyl-1,3-thiazole-4-carboxylate (6.63 g) as an off-white solid.

10 mp. 208-208.5°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 3.67 (3H, s), 7.38-7.53 (5H, m).

MS: 235 ( $\text{M}+\text{H}$ )<sup>+</sup>

### Step 3

Methyl 2-amino-5-phenyl-1,3-thiazole-4-carboxylate (3 g)  
15 was dissolved in pyridine (30 ml), and then acetyl chloride (2.73 ml) was added dropwise to the solution at 0°C under  $\text{N}_2$  atmosphere. The reaction mixture was stirred at r.t. for 1.5 hours. Water was added to the solution at 0°C. The precipitate was filtered *in vacuo*, and the solid was washed  
20 with ethyl ether to give methyl 2-(acetylamino)-5-phenyl-1,3-thiazole-4-carboxylate (2.37 g) as a pale brown solid.

mp. 224.5-225.5°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.16 (3H, s), 3.68 (3H, s), 7.39-7.57 (5H, m), 12.56 (1H, s).

25 MS: 277 ( $\text{M}+\text{H}$ )<sup>+</sup>

### Step 4

Methyl 2-(acetylamino)-5-phenyl-1,3-thiazole-4-carboxylate (2.34 g) was suspended in THF (23 ml), and then lithium aluminium hydride (482 mg) was added portionwise to  
30 the solution at 0°C. The reaction mixture was stirred at 0°C for 1.5 hours and quenched with MeOH. AcOEt and 1N HCl were added to the mixture, and the mixture was extracted. The aqueous layer was extracted with AcOEt (twice). The combined

organic layer was washed with brine, dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residual solid was dissolved in MeOH (5 ml) and  $\text{CHCl}_3$  (90 ml). Then manganese(IV) oxide (11 g) was added to the solution under  $\text{N}_2$  atmosphere.

5 The reaction mixture was stirred at r.t. for 13 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with  $\text{CHCl}_3$  / MeOH (20:1) as an eluent to give N-(4-formyl-5-phenyl-1,3-thiazol-2-yl)acetamide

10 (705.2 mg) as a brown amorphous substance.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.19 (3H, s), 7.49-7.58 (3H, m), 7.60-7.69 (2H, m), 9.78 (1H, s), 12.60 (1H, s).

MS: 247 ( $\text{M}+\text{H}$ ) $^+$

#### Step 5

15 1-(Bromomethyl)-4-nitrobenzene (1.03 g), triphenylphosphine (1.25 g) and DMF (14 ml) were combined under  $\text{N}_2$  atmosphere. The reaction mixture was stirred at r.t. for 6 hours. Then potassium tert-butoxide (629 mg) and N-(4-formyl-5-phenyl-1,3-thiazol-2-yl)acetamide (690 mg) were added

20 to the mixture, and the mixture was stirred at r.t. for 13 hours. The reaction mixture was poured into ice-water, and extracted with AcOEt. The organic layer was washed with 1N-HCl, water and brine, dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified by flash

25 column chromatography over silica gel with  $\text{CHCl}_3$  / AcOEt (1:1) as an eluent to give a mixture of N-{4-[(E)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide and N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide (E : Z = 2 : 1) (1.02 g) as an orange wax.

30  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.13 (3Hx1/3, s), 2.19 (3Hx2/3, s), 6.65 (1Hx1/3, d, J=12.5Hz), 6.78 (1Hx1/3, d, J=12.5Hz), 7.32 (1Hx2/3, d, J=15.5Hz), 7.39-7.59 (5H+1Hx2/3, m), 7.61 (2Hx1/3, d, J=9.0Hz), 7.77 (2Hx2/3, d, J=9.0Hz),

8.13 (2Hx1/3, d, J=9.0Hz), 8.19 (2Hx2/3, d, J=9.0Hz), 12.33 (1H, brs).

MS: 366 (M+H)<sup>+</sup>

Step 6

5 A mixture of N-{4-[(E)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide and N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-5-phenyl-1,3-thiazol-2-yl}acetamide (E : Z = 2 : 1) (600 mg), 10% palladium carbon (657 mg), MeOH (6 ml), THF (6 ml) and AcOH (1 ml) were combined. The reaction mixture  
10 was stirred under 3 atm H<sub>2</sub> at r.t. for 3.5 hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. 1N-NaOH was added to the residue, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give  
15 N-{4-[2-(4-aminophenyl)ethyl]-5-phenyl-1,3-thiazol-2-yl}acetamide (528.6mg) as a pale brown amorphous substance.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15 (3H, s), 2.80 (4H, s), 4.82 (2H, s), 6.45 (2H, d, J=8.5Hz), 6.78 (2H, d, J=8.5Hz), 7.21-7.44 (5H, m), 12.18 (1H, brs).

20 MS: 338 (M+H)<sup>+</sup>

Step 7

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-phenyl-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production  
25 Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.21 (9H, s), 1.44 (9H, s), 2.15 (3H, s), 2.83-2.98 (4H, m), 7.10 (2H, d, J=8.5Hz), 7.22-7.47 (7H, m), 9.92 (1H, s), 11.43 (1H, s), 12.22 (1H, s).

MS: 580 (M+H)<sup>+</sup>

30 Step 8

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 80-82°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.83-3.08(4H, m), 7.11(2H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 7.29-7.54(8H, m), 9.94(1H, s), 12.22(1H, brs).

MS: 380(M+H)<sup>+</sup> free

<sup>5</sup> **Production Example 46**: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-benzyl-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

To a suspension of copper(II) bromide (9.75 g) in AcOEt  
<sup>10</sup> (150 ml) was added a solution of ethyl 2-oxo-4-phenylbutanoate (3 g) in 75 ml of CHCl<sub>3</sub>. The reaction mixture was refluxed for 23 hours, cooled to r.t., and filtered through a short pad of silica gel eluting with AcOEt / n-hexane (1:1). The solvent was removed *in vacuo* to give ethyl 3-bromo-2-oxo-4-  
<sup>15</sup> phenylbutanoate (4.2g) as a yellow liquid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.37(3H, t, J=7.0Hz), 3.25(1H, dd, J=14.5, 7.5Hz), 3.54(1H, dd, J=14.5, 7.5Hz), 4.35(2H, q, J=7.0Hz), 5.27(1H, d, J=7.5Hz), 7.18-7.41(5H, m).

Step 2

<sup>20</sup> Ethyl 3-bromo-2-oxo-4-phenylbutanoate (5.8 g) was dissolved in EtOH (110 ml), and then thiourea (3.1 g) was added to the solution. The reaction mixture was refluxed for 2 hours under N<sub>2</sub> atmosphere. The cooled reaction mixture was evaporated *in vacuo*. The residual solid was suspended (pH=8)  
<sup>25</sup> in saturated NaHCO<sub>3</sub> and water. The solid was collected by filtration, and purified by flash column chromatography over silica gel with CHCl<sub>3</sub> / MeOH (10:1) as an eluent to give ethyl 2-amino-5-benzyl-1,3-thiazole-4-carboxylate (808.2 mg) as a yellow wax.

<sup>30</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.25(3H, t, J=7.0Hz), 4.21(2H, q, J=7.0Hz), 4.33(2H, s), 7.02(2H, s), 7.11-7.39(5H, m).

MS: 263(M+H)<sup>+</sup>

Step 3

Ethyl 2-(acetylamino)-5-benzyl-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 3 of Production Example 45.

mp. 178-180°C

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.28 (3H, t, J=7.0Hz), 2.09 (3H, s), 4.28 (2H, q, J=7.0Hz), 4.48 (2H, s), 7.19-7.39 (5H, m), 12.41 (1H, s).

MS: 305 (M+H)<sup>+</sup>

#### Step 4

<sup>10</sup> Ethyl 2-(acetylamino)-5-benzyl-1,3-thiazole-4-carboxylate (1.0 g) was dissolved in THF (20 ml), and then lithium borohydride (124 mg) was added portionwise to the solution at 0°C. The reaction mixture was refluxed for 4.5 hours and quenched with MeOH. The mixture was concentrated *in vacuo*, and  
<sup>15</sup> purified by flash column chromatography over silica gel with CHCl<sub>3</sub> / MeOH (20:1) as an eluent. The residual amorphous substance was dissolved in MeOH (1 ml) and CHCl<sub>3</sub> (8 ml). Then manganese(IV) oxide (1.26 g) was added to the solution under N<sub>2</sub> atmosphere. The reaction mixture was stirred at r.t. for 12  
<sup>20</sup> hours, and filtered through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with CHCl<sub>3</sub> / MeOH (20:1) as an eluent to give N-(5-benzyl-4-formyl-1,3-thiazol-2-yl)acetamide (251 mg) as a pale yellow solid.

<sup>25</sup> mp. 191-192.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12 (3H, s), 4.53 (2H, s), 7.19-7.40 (5H, m), 10.04 (1H, s), 12.34 (1H, s).

MS: 261 (M+H)<sup>+</sup>

#### Step 5

<sup>30</sup> N-{5-Benzyl-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

Z : E = 2 : 1

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08 (3Hx2/3, s), 2.12 (3Hx1/3, s), 4.08 (2Hx2/3, s), 4.34 (2Hx1/3, s), 6.72 (1Hx2/3, d, J=12.5Hz), 6.86 (1Hx2/3, d, J=12.5Hz), 7.17-7.39 (5H+2Hx1/3, m), 7.66 (2Hx2/3, d, J=9.0Hz), 7.92 (2Hx1/3, d, J=9.0Hz),  
5 8.14 (2Hx2/3, d, J=9.0Hz), 8.22 (2Hx1/3, d, J=9.0Hz), 11.85 (1Hx2/3, s), 12.16 (1Hx1/3, s).

MS: 380 (M+H)<sup>+</sup>

#### Step 6

N-{4-[2-(4-Aminophenyl)ethyl]-5-benzyl-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to  
10 Step 6 of Production Example 45.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.07 (3H, s), 2.59-2.85 (4H, m), 3.85 (2H, s), 4.84 (2H, s), 6.46 (2H, d, J=8.5Hz), 6.78 (2H, d, J=8.5Hz), 7.07 (2H, d, J=8.0Hz), 7.16-7.31 (3H, m), 11.96 (1H,  
15 s).

MS: 352 (M+H)<sup>+</sup>

#### Step 7

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-benzyl-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was  
20 prepared in a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39 (9H, s), 1.51 (9H, s), 2.07 (3H, s), 2.85 (4H, s), 3.89 (2H, s), 7.05-7.33 (7H, m), 7.42 (2H, d, J=8.5Hz), 9.95 (1H, s), 11.44 (1H, s), 11.99 (1H, s).

25 MS: 594 (M+H)<sup>+</sup>

#### Step 8

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

mp. 97-99°C

30 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09 (3H, s), 2.86 (4H, s), 3.93 (2H, s), 7.05-7.37 (9H, m), 7.47 (3H, s), 9.98 (1H, s), 12.01 (1H, brs).

MS: 394 (M+H)<sup>+</sup> free

**Production Example 47:** Synthesis of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

5        3-(4-Mercaptophenyl)propanoic acid (5 g),  $K_2CO_3$  (11.4 g) and DMF (30 ml) were combined, and iodomethane (5.12 ml) was added dropwise to the mixture at 0°C under  $N_2$  atmosphere. The reaction mixture was stirred at r.t. for 13 hours, and poured into ice-water. The mixture was extracted with AcOEt. The  
10    organic layer was washed with water (twice) and brine, dried over anhydrous  $MgSO_4$ , and concentrated *in vacuo* to give methyl 3-[4-(methylthio)phenyl]propanoate (4.19 g) as pale yellow oil.

$^1H$ -NMR ( $CDCl_3$ ),  $\delta$  (ppm): 2.47(3H, s), 2.61(2H, t,  $J=8.0Hz$ ),  
15    2.91(2H, t,  $J=8.0Hz$ ), 3.67(3H, s), 7.12(2H, d,  $J=8.5Hz$ ), 7.20(2H, d,  $J=8.5Hz$ ).

Step 2

Sodium methoxide, 28% solution in MeOH (3.67 ml), was added dropwise to the mixture of methyl 3-[4-(methylthio)phenyl]propanoate (4 g) and diethyl oxalate (5.17  
20    ml) at 0°C with stirring. The reaction mixture was stirred at 65°C for 30 minutes under reduced pressure. 15% Aqueous  $H_2SO_4$  (35 ml) was added to the mixture, and the mixture was refluxed for 15 hours. After cooled to r.t., the mixture was extracted  
25    with AcOEt. The organic layer was washed with water and brine, dried over anhydrous  $MgSO_4$ , and concentrated *in vacuo*. The residual oil was dissolved in EtOH (20 ml), and concentrated  $H_2SO_4$  (0.4 ml) was added dropwise to the solution. The reaction mixture was refluxed for 2 hours. After cooled to r.t., EtOH  
30    was removed *in vacuo*. AcOEt and water were added to the residue, and extracted. The organic layer was washed with water and brine, dried over anhydrous  $MgSO_4$ , and concentrated *in vacuo*. The residue was purified by flash column

chromatography over silica gel with *n*-hexane / AcOEt (6:1) as an eluent to give ethyl 4-[4-(methylthio)phenyl]-2-oxobutanoate (2.43 g) as a yellow liquid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.35(3H, t, J=7.0Hz), 2.46(3H, s),  
5 2.92(2H, t, J=7.0Hz), 3.16(2H, t, J=7.0Hz), 4.31(2H, q, J=7.0Hz), 7.13(2H, d, J=8.5Hz), 7.20(2H, d, J=8.5Hz).

### Step 3

Ethyl 3-bromo-4-[4-(methylthio)phenyl]-2-oxobutanoate was prepared in a similar manner according to Step 1 of Production  
10 Example 46.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.37(3H, t, J=7.0Hz), 2.47(3H, s),  
3.20(1H, dd, J=14.5, 7.5Hz), 3.49(1H, dd, J=14.5, 7.5Hz),  
4.35(2H, q, J=7.0Hz), 5.22(1H, d, J=7.5Hz), 7.17(2H, d, J=8.5Hz), 7.20(2H, d, J=8.5Hz).

### 15 Step 4

Ethyl 2-amino-5-[4-(methylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 2 of Production Example 46.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.25(3H, t, J=7.0Hz), 2.44(3H, s),  
20 4.20(2H, q, J=7.0Hz), 4.28(2H, s), 7.02(2H, s), 7.19(4H, s).  
MS: 309(M+H)<sup>+</sup>

### Step 5

Ethyl 2-(acetylamino)-5-[4-(methylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner  
25 according to Step 3 of Production Example 45.

mp. 205-206°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.28(3H, t, J=7.0Hz), 2.09(3H, s),  
2.45(3H, s), 4.27(2H, q, J=7.0Hz), 4.43(2H, s), 7.22(4H, s),  
12.41(1H, s).  
30 MS: 351(M+H)<sup>+</sup>

### Step 6

N-{4-Formyl-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to

Step 4 of Production Example 46.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.12 (3H, s), 2.45 (3H, s), 4.48 (2H, s), 7.23 (4H, s), 10.03 (1H, s), 12.33 (1H, s).

MS: 307 ( $\text{M}+\text{H}$ ) $^+$

5 Step 7

N-{5-[4-(Methylthio)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

Z : E = 2 : 1

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.08 (3Hx2/3, s), 2.12 (3Hx1/3, s), 2.44 (3H, s), 4.04 (2Hx2/3, s), 4.30 (2Hx1/3, s), 6.71 (1Hx2/3, d, J=12.5Hz), 6.84 (1Hx2/3, d, J=12.5Hz), 7.18 (4Hx2/3, s), 7.23 (4Hx1/3, s), 7.24 (1Hx1/3, d, J=15.5Hz), 7.40 (1Hx1/3, d, J=15.5Hz), 7.65 (2Hx2/3, d, J=9.0Hz), 7.92 (2Hx1/3, d, J=9.0Hz), 8.12 (2Hx2/3, d, J=9.0Hz), 8.22 (2Hx1/3, d, J=9.0Hz), 11.85 (1Hx2/3, brs), 12.16 (1Hx1/3, brs).

MS: 426 ( $\text{M}+\text{H}$ ) $^+$

Step 8

N-{5-[4-(Methylsulfonyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 2 of Production Example 32.

Z : E = 2 : 1

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.09 (3Hx2/3, s), 2.13 (3Hx1/3, s), 3.18 (3H, s), 4.24 (2Hx2/3, s), 4.49 (2Hx1/3, s), 6.73 (1Hx2/3, d, J=12.5Hz), 6.86 (1Hx2/3, d, J=12.5Hz), 7.33 (1Hx1/3, d, J=15.5Hz), 7.41-7.97 (5/3H, m), 7.48 (2Hx2/3, d, J=9.0Hz), 7.55 (2Hx1/3, d, J=9.0Hz), 7.65 (2Hx2/3, d, J=9.0Hz), 7.85 (2Hx2/3, d, J=9.0Hz), 8.14 (2Hx2/3, d, J=9.0Hz), 8.22 (2Hx1/3, d, J=9.0Hz), 11.90 (1Hx2/3, s), 12.22 (1Hx1/3, s).

MS: 458 ( $\text{M}+\text{H}$ ) $^+$

Step 9

The title compound was prepared in a similar manner according to Step 6 of Production Example 45.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08 (3H, s), 2.58-2.87 (4H, m), 3.18 (3H, s), 3.98 (2H, s), 4.85 (2H, s), 6.46 (2H, d, J=8.5Hz), 6.77 (2H, d, J=8.5Hz), 7.27 (2H, d, J=8.5Hz), 7.82 (2H, d, J=8.5Hz), 12.02 (1H, s).

<sup>5</sup> MS: 430 (M+H)<sup>+</sup>

**Production Example 48:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

<sup>10</sup> Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound obtained in Example 47 in a similar manner according to Step 3 of Production Example 31.

<sup>15</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39 (9H, s), 1.51 (9H, s), 2.08 (3H, s), 2.86 (4H, s), 3.16 (3H, s), 4.03 (2H, s), 7.13 (2H, d, J=8.5Hz), 7.33 (2H, d, J=8.5Hz), 7.43 (2H, d, J=8.5Hz), 7.81 (2H, d, J=8.5Hz), 9.97 (1H, s), 11.45 (1H, s), 12.05 (1H, s).

MS: 672 (M+H)<sup>+</sup>

<sup>20</sup> Step 2

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate (953 mg) and 4N HCl in 1,4-dioxane solution (10 ml) were combined under N<sub>2</sub>  
<sup>25</sup> atmosphere. The reaction mixture was stirred at r.t. for 7 hours. The solvent was removed *in vacuo*. The residue was dissolved in water and AcOEt. The solution was made basic (pH=8) by saturated NaHCO<sub>3</sub>. The precipitate was filtered *in vacuo* to give N-{4-[2-(4-  
<sup>30</sup> {[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (667.7 mg) as a pale yellow solid.

mp. 228-229.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08 (3H, s), 2.79 (4H, m), 3.18 (3H, s), 4.05 (2H, s), 6.72 (2H, d, J=8.0Hz), 6.99 (2H, d, J=8.0Hz), 7.37 (2H, d, J=8.5Hz), 7.84 (2H, d, J=8.5Hz).

MS: 472 (M+H)<sup>+</sup>

5 **Production Example 49:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide hydrochloride

The title compound was prepared from the compound  
10 obtained in Step 1 of Production Example 48 in a similar manner according to Step 4 of Production Example 31.

mp. 107-110°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09 (3H, s), 2.87 (4H, s), 3.19 (3H, s), 4.08 (2H, s), 7.13 (2H, d, J=8.5Hz), 7.25 (2H, d, J=8.5Hz),  
15 7.40 (2H, d, J=8.5Hz), 7.44 (3H, s), 7.85 (2H, d, J=8.5Hz), 9.94 (1H, s), 12.05 (1H, brs).

MS: 472 (M+H)<sup>+</sup> free

**Production Example 50:** Synthesis of N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide  
20 Step 1

To a ice-cold solution of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (247.6 mg) in acetone (4.8 ml) was added benzoyl isothiocyanate (94.1  
25 mg), and the mixture was stirred at r.t. for 1 hour. Water was added to the mixture, and the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residual amorphous substance was dissolved in EtOH (5 ml), and  
30 6N-NaOH (0.288 ml) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 2 hours, and neutralized with 1N-HCl at 0°C. The mixture was extracted with AcOEt. The organic layer was washed with water and brine,

dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was solidified with ethyl ether to give N-{4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (290.7 mg) as an off-white solid.

mp. 102-103°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.09 (3H, s), 2.85 (4H, s), 3.18 (3H, s), 4.03 (2H, s), 7.11 (2H, d,  $J=8.5\text{Hz}$ ), 7.30 (2H, d,  $J=8.5\text{Hz}$ ), 7.36 (2H, d,  $J=8.5\text{Hz}$ ), 7.84 (2H, d,  $J=8.5\text{Hz}$ ), 9.64 (1H, s), 12.04 (1H, s).

MS: 489 ( $\text{M}+\text{H}$ )<sup>+</sup>

### Step 2

A mixture of N-{4-(2-{4-[(aminocarbonothioyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (281.8 mg), methyl iodide (0.0431 ml) and MeOH (3 ml) was refluxed for 3.5 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with AcOEt and stirred for 30 minutes. The precipitated crystals were filtered and washed with AcOEt to give methyl N-[4-(2-{2-(acetyl amino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]imidothiocarbamate hydroiodide (291.5 mg) as an off-white amorphous solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.09 (3H, s), 2.68 (3H, s), 2.90 (4H, s), 3.18 (3H, s), 4.07 (2H, s), 7.22 (2H, d,  $J=8.5\text{Hz}$ ), 7.32 (2H, d,  $J=8.5\text{Hz}$ ), 7.39 (2H, d,  $J=8.5\text{Hz}$ ), 7.86 (2H, d,  $J=8.5\text{Hz}$ ), 9.22 (1H, brs), 11.11 (1H, brs), 12.03 (1H, s).

MS: 503 ( $\text{M}+\text{H}$ )<sup>+</sup> free

### Step 3

The title compound was prepared in a similar manner according to the following Production Example 58.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.09 (3H, s), 2.87 (4H, s), 3.19 (3H, s), 4.08 (2H, s), 7.12 (2H, d,  $J=8.5\text{Hz}$ ), 7.23 (2H, d,  $J=8.5\text{Hz}$ ),

7.41(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz), 8.92(2H, brs),  
12.03(1H, brs).

MS: 487 (M+H)<sup>+</sup>

**Production Example 51:** Synthesis of N-{4-[2-(4-  
5 { [amino(imino)methyl]amino}phenyl)ethyl]-5-[4-  
(ethylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide  
hydrochloride

Step 1

Ethyl 3-[4-(ethylthio)phenyl]propanoate was prepared from  
10 4-(2-carboxyethyl)thiophenol in a similar manner according to  
Step 1 of Production Example 47.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.23(3H, t, J=7.0Hz), 1.29(3H, t,  
J=7.0Hz), 2.60(2H, t, J=8.5Hz), 2.82-2.99(4H, m), 4.12(2H, q,  
J=7.0Hz), 7.12(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz).

15 Step 2

Ethyl 4-[4-(ethylthio)phenyl]-2-oxobutanoate was prepared  
in a similar manner according to Step 2 of Production Example  
47.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.31(3H, t, J=7.0Hz), 1.36(3H, t,  
20 J=7.0Hz), 2.92(2H, q, J=7.0Hz), 2.93(2H, t, J=7.0Hz), 3.16(2H,  
t, J=7.0Hz), 4.27(2H, q, J=7.0Hz), 7.08(2H, d, J=9.0Hz),  
7.26(2H, d, J=9.0Hz).

Step 3

Ethyl 3-bromo-4-[4-(ethylthio)phenyl]-2-oxobutanoate was  
25 prepared in a similar manner according to Step 1 of Production  
Example 46.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.31(3H, t, J=7.5Hz), 1.38(3H, t,  
J=7.5Hz), 2.93(2H, q, J=7.5Hz), 3.21(1H, dd, J=14.5, 7.5Hz),  
3.49(1H, dd, J=14.5, 7.5Hz), 4.35(2H, q, J=7.5Hz), 5.23(1H, t,  
30 J=7.5Hz), 7.16(2H, d, J=8.5Hz), 7.27(2H, d, J=8.5Hz).

Step 4

Ethyl 2-amino-5-[4-(ethylthio)benzyl]-1,3-thiazole-4-  
carboxylate was prepared in a similar manner according to Step

2 of Production Example 46.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.22 (6H, t, J=7.0Hz), 2.94 (2H, q, J=7.0Hz), 4.20 (2H, q, J=7.0Hz), 4.29 (2H, s), 7.03 (2H, s), 7.18 (2H, d, J=8.5Hz), 7.26 (2H, d, J=8.5Hz).

5 MS: 323 (M+H)<sup>+</sup>

#### Step 5

Ethyl 2-(acetylamino)-5-[4-(ethylthio)benzyl]-1,3-thiazole-4-carboxylate was prepared in a similar manner according to Step 3 of Production Example 45.

10 mp. 189.5-190°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.21 (3H, t, J=7.5Hz), 1.28 (3H, t, J=7.0Hz), 2.09 (3H, s), 2.95 (2H, q, J=7.5Hz), 4.27 (2H, q, J=7.0Hz), 4.44 (2H, s), 7.22 (2H, d, J=8.5Hz), 7.26 (2H, d, J=8.5Hz), 12.42 (1H, s).

15 MS: 365 (M+H)<sup>+</sup>

#### Step 6

N-{5-[4-(Ethylthio)benzyl]-4-formyl-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 4 of Production Example 46.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.21 (3H, t, J=7.5Hz), 2.17 (3H, s), 2.95 (2H, q, J=7.5Hz), 4.49 (2H, s), 7.26 (4H, s), 10.03 (1H, s), 12.34 (1H, s).

#### Step 7

N-{5-[4-(Ethylthio)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

Z : E = 3 : 2

30 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.20 (3H, t, J=7.5Hz), 2.08 (3Hx3/5, s), 2.12 (3Hx2/5, s), 2.93 (2H, q, J=7.5Hz), 4.05 (2Hx3/5, s), 4.31 (2Hx2/5, s), 6.71 (1Hx3/5, d, J=12.5Hz), 6.84 (1Hx3/5, d, J=12.5Hz), 7.13-8.16 (6H+4/5H, m), 8.12 (2Hx3/5, d, J=9.0Hz), 8.22 (2Hx2/5, d, J=9.0Hz), 11.86 (1Hx3/5, brs), 12.18 (1Hx2/5, brs).

MS: 440 (M+H)<sup>+</sup>

Step 8

N-{5-[4-(Ethylsulfonyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in  
5 a similar manner according to Step 2 of Production Example 32.

Z : E = 3 : 2

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.06(3H, t, J=7.5Hz), 2.09(3Hx3/5, s), 2.13(3Hx2/5, s), 3.25(2H, q, J=7.5Hz), 4.24(2Hx3/5, s), 4.50(2Hx2/5, s), 6.73(1Hx3/5, d, J=12.5Hz), 6.87(1Hx3/5, d, J=12.5Hz), 7.43-8.31(8H+4/5H, m), 11.91(1Hx3/5, brs),  
10 12.22(1Hx2/5, brs).

MS: 472 (M+H)<sup>+</sup>

Step 9

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(ethylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared in  
15 a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.05(3H, t, J=7.5Hz), 1.39(9H, s), 1.51(9H, s), 2.09(3H, s), 2.85(4H, s), 3.22(2H, q, J=7.5Hz),  
20 4.04(2H, s), 7.11(2H, d, J=8.5Hz), 7.32(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz), 7.77(2H, d, J=8.5Hz), 9.97(1H, s), 11.44(1H, s), 12.05(1H, s).

MS: 686 (M+H)<sup>+</sup>

Step 10

25 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.07(3H, t, J=7.5Hz), 2.09(3H, s), 2.86(4H, s), 3.26(2H, q, J=7.5Hz), 4.09(2H, s), 7.13(2H, d, J=8.0Hz), 7.24(2H, d, J=8.0Hz), 7.44(3H, brs), 7.60(2H, d, J=8.0Hz), 7.81(2H, d, J=8.0Hz), 9.89(1H, s), 12.05(1H, brs).  
30

MS: 486 (M+H)<sup>+</sup> free

Production Example 52: Synthesis of ethyl {4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-

(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate

Step 1

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (300 mg) was dissolved in THF (3 ml) under N<sub>2</sub> atmosphere. Then di(tert-butyl)dicarbonate (168 mg) in THF (3 ml) was added to the solution at r.t. The reaction mixture was stirred at r.t. for 14 hours, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with CHCl<sub>3</sub> / AcOEt (1:1) as an eluent to give tert-butyl [4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (248.5 mg) as an off-white amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.47 (9H, s), 2.08 (3H, s), 2.82 (4H, s), 3.16 (3H, s), 3.99 (2H, s), 7.00 (2H, d, J=8.5Hz), 7.25 (2H, d, J=8.5Hz), 7.33 (2H, d, J=8.5Hz), 7.79 (2H, d, J=8.5Hz), 9.24 (1H, s), 12.03 (1H, s).

MS: 530 (M+H)<sup>+</sup>

Step 2

tert-Butyl [4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (230 mg), 1N-NaOH (1.09 ml) and EtOH (5 ml) were combined, and the mixture was refluxed for 16 hours. After cooled to r.t., the organic solvent was removed *in vacuo*. The aqueous solution was neutralized with 1N-HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with CHCl<sub>3</sub> / MeOH (30:1) as an eluent to give tert-butyl [4-(2-{2-amino-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (151.2 mg) as an off-white amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.47 (9H, s), 2.58-2.82 (4H, m),

3.16(3H, s), 3.84(2H, s), 6.73(2H, s), 7.02(2H, d, J=8.5Hz), 7.21(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.77(2H, d, J=8.5Hz), 9.24(1H, s).

MS: 488 (M+H)<sup>+</sup>

<sup>5</sup> Step 3

tert-Butyl [4-(2-{2-amino-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]carbamate (140 mg) was dissolved in pyridine (2 ml) under N<sub>2</sub> atmosphere. Then, ethyl chloroformate (30.2 ml) was added to the solution at 0°C. The reaction mixture was stirred at r.t. for 2 hours, and concentrated *in vacuo*. The residue was dissolved in AcOEt, and washed with 1N-HCl, water and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo* to give ethyl {4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate (155.8 mg) as an off-white amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.21(3H, t, J=7.0Hz), 1.47(9H, s), 2.79(4H, s), 3.16(3H, s), 3.97(2H, s), 4.14(2H, q, J=7.0Hz), 7.00(2H, d, J=8.5Hz), 7.24(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz), 9.54(1H, s), 11.64(1H, brs).

MS: 560 (M+H)<sup>+</sup>

Step 4

Ethyl {4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate (140 mg) and 4N HCl in 1,4-dioxane solution (3 ml) were combined under N<sub>2</sub> atmosphere. The reaction mixture was stirred at r.t. for 2 hours. The solvent was removed *in vacuo*. The residue was dissolved in water and AcOEt. The mixture was made basic (pH=8) by 1N-NaOH. The organic layer was washed with water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo* to give ethyl {4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}carbamate (125.6mg) as an off-white amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.21 (3H, t, J=7.0Hz), 2.60-2.80 (4H, m), 3.18 (3H, s), 3.97 (2H, s), 4.14 (2H, q, J=7.0Hz), 4.85 (2H, brs), 6.46 (2H, d, J=8.5Hz), 6.77 (2H, d, J=8.5Hz), 7.29 (2H, d, J=8.5Hz), 7.82 (2H, d, J=8.5Hz), 11.62 (1H, brs).

5 MS: 460 (M+H)<sup>+</sup>

#### Step 5

Di-tert-butyl ((Z)-{[4-(2-{2-[(ethoxycarbonyl)amino]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylenidene)biscarbamate was prepared in  
10 a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.21 (3H, t, J=7.0Hz), 1.39 (9H, s), 1.51 (9H, s), 2.84 (4H, s), 3.16 (3H, s), 4.01 (2H, s), 4.14 (2H, q, J=7.0Hz), 7.13 (2H, d, J=8.5Hz), 7.33 (2H, d, J=8.5Hz), 7.43 (2H, d, J=8.5Hz), 7.81 (2H, d, J=8.5Hz), 9.97 (1H, s),  
15 11.45 (1H, s), 11.61 (1H, brs).

MS: 702 (M+H)<sup>+</sup>

#### Step 6

The title compound was prepared in a similar manner according to Step 2 of Production Example 48.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.17 (3H, t, J=7.0Hz), 2.57 (4H, s), 3.17 (3H, s), 4.01 (2H, q, J=7.0Hz), 4.03 (2H, s), 7.00 (4H, s), 7.42 (2H, d, J=8.5Hz), 7.83 (2H, d, J=8.5Hz).

MS: 502 (M+H)<sup>+</sup>

**Production Example 53:** Synthesis of N-{4-{2-[4-(aminomethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

#### Step 1

[4-(Methoxycarbonyl)benzyl](triphenyl)phosphonium bromide (4.81 g) and DMF (60 ml) were combined under N<sub>2</sub> atmosphere.  
30 Then potassium tert-butoxide (1.32 g) and N-{4-formyl-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide (3 g) were added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 18 hours, poured into ice-water, and

extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with  $\text{CHCl}_3$  / AcOEt (2:1) as an eluent. The solid was suspended in AcOEt, and the suspension was filtered. The filtrate was concentrated *in vacuo* to give methyl 4-((Z)-2-{2-(acetylamino)-5-[4-(methylthio)benzyl]-1,3-thiazol-4-yl}vinyl)benzoate (4.16 g) as a yellow amorphous substance.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.08 (3H, s), 2.43 (3H, s), 3.84 (3H, s), 3.96 (2H, s), 6.67 (1H, d,  $J=12.5\text{Hz}$ ), 6.74 (1H, d,  $J=12.5\text{Hz}$ ), 7.11 (2H, d,  $J=8.5\text{Hz}$ ), 7.17 (2H, d,  $J=8.5\text{Hz}$ ), 7.50 (2H, d,  $J=8.5\text{Hz}$ ), 7.85 (2H, d,  $J=8.5\text{Hz}$ ), 11.88 (1H, s).

MS: 439 ( $\text{M}+\text{H}$ )<sup>+</sup>

### Step 2

Methyl 4-((Z)-2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}vinyl)benzoate was prepared in a similar manner according to Step 2 of Production Example 32.

Z : E = 2 : 1

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.08 (3Hx2/3, s), 2.12 (3Hx1/3, s), 3.18 (3H, s), 3.84 (3Hx2/3, s), 3.86 (3Hx1/3, s), 4.15 (2Hx2/3, s), 4.47 (2Hx1/3, s), 6.68 (1Hx2/3, d,  $J=12.5\text{Hz}$ ), 6.77 (1Hx2/3, d,  $J=12.5\text{Hz}$ ), 7.30 (1Hx1/3, d,  $J=15.5\text{Hz}$ ), 7.43 (2H, d,  $J=8.5\text{Hz}$ ), 7.50-7.97 (19/3H, m), 11.93 (1Hx2/3, s), 12.19 (1Hx1/3, s).

MS: 471 ( $\text{M}+\text{H}$ )<sup>+</sup>

### Step 3

Methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

mp. 209-210°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.09 (3H, s), 2.94 (4H, m), 3.17 (3H, s), 3.84 (3H, s), 4.01 (2H, s), 7.25 (2H, d,  $J=8.5\text{Hz}$ ), 7.28 (2H,

d, J=8.5Hz), 7.76(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz), 12.05(1H, brs).

MS: 473(M+H)<sup>+</sup>

#### Step 4

5 To a stirred solution of methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)benzoate (2 g) in dry THF (40 ml) was added dropwise 1.0M diisobutylaluminium hydride solution in toluene (14.8 ml) at -78°C under N<sub>2</sub> atmosphere. The reaction mixture was stirred at  
10 r.t. for 4 hours, and then quenched with MeOH. AcOEt and 1N-HCl were added to the mixture, and extracted. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with CHCl<sub>3</sub> / MeOH (20:1)  
15 as an eluent to give N-{4-{2-[4-(hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (552.3 mg) as a colorless solid.

mp. 209.5-211°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.86(4H, s), 3.17(3H, s), 4.01(2H, s), 4.46(2H, d, J=5.5Hz), 5.12(1H, t, J=5.5Hz),  
20 7.09(2H, d, J=8.0Hz), 7.20(2H, d, J=8.0Hz), 7.28(2H, d, J=8.5Hz), 7.80(2H, d, J=8.5Hz), 12.04(1H, brs).

MS: 445(M+H)<sup>+</sup>

#### Step 5

25 N-{4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (539.5 mg), CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and DMF (5 ml) were combined under N<sub>2</sub> atmosphere. Then, Et<sub>3</sub>N (0.211 ml) and MsCl (0.108 ml) were added to the suspension at 0°C. The reaction mixture was stirred at r.t.  
30 for 3.5 hours. The reaction mixture was poured into water, and extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residual solid was washed with ethyl ether to give N-{4-{2-[4-

(chloromethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (537.5 mg) as an off-white solid.

mp. 202-203°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.88(4H, s), 3.17(3H, s), 4.01(2H, s), 4.73(2H, s), 7.15(2H, d, J=8.0Hz), 7.30(2H, d, J=8.5Hz), 7.34(2H, d, J=8.0Hz), 7.81(2H, d, J=8.5Hz), 12.05(1H, brs).

MS: 463 (M+H)<sup>+</sup>

#### Step 6

N-{4-{2-[4-(Chloromethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (150 mg) was suspended in CH<sub>3</sub>CN (6 ml), and then 28% ammonia solution (0.4 ml) was added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 16 hours, and concentrated *in vacuo*. The residual solid was washed with water, and purified by preparative silica gel chromatography with CHCl<sub>3</sub> / MeOH (10:1) as an eluent to give N-{4-{2-[4-(aminomethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (32.1mg) as a pale yellow amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.85(4H, s), 3.17(3H, s), 3.69(2H, s), 4.01(2H, s), 7.07(2H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 7.29(2H, d, J=8.5Hz), 7.80(2H, d, J=8.5Hz).

MS: 444 (M+H)<sup>+</sup>

**Production Example 54:** Synthesis of N-{4-{2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

A mixture of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}-acetamide (200 mg), 2-(methylsulfonyl)-4,5-dihydro-1,3-thiazole (62 mg), concentrated HCl (0.064 ml) and 2-methoxyethanol (3 ml) was stirred at 120°C for 13 hours under N<sub>2</sub> atmosphere. After cooled to r.t., the reaction mixture was made basic with

saturated  $\text{NaHCO}_3$ . The mixture was extracted with  $\text{AcOEt}$ . The organic layer was dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography with  $\text{CHCl}_3$  /  $\text{MeOH}$  (10:1) as an eluent to give N-  
5 {4-{2-[4-(4,5-dihydro-1,3-thiazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (139.8 mg) as a pale yellow amorphous substance.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.08 (3H, s), 2.82 (4H, s), 3.16 (3H, s), 3.17-3.34 (4H, m), 3.98 (2H, s), 6.99 (2H, d,  $J=8.5\text{Hz}$ ),  
10 7.25 (2H, d,  $J=8.5\text{Hz}$ ), 7.45 (2H, brd,  $J=8.5\text{Hz}$ ), 7.80 (2H, d,  $J=8.5\text{Hz}$ ), 9.24 (1H, brs), 12.04 (1H, s).

MS: 515 ( $\text{M}+\text{H}$ ) $^+$

**Production Example 55:** Synthesis of N-{4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide  
15

A mixture of N-{4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (150 mg), ethyl 2-(methylthio)-4,5-dihydro-1H-imidazole-1-carboxylate (78.9 mg),  $\text{AcOH}$  (0.3 ml) and  $\text{EtOH}$  (3 ml) was refluxed for 7  
20 hours under  $\text{N}_2$  atmosphere. After cooled to r.t., the reaction mixture was made basic with saturated  $\text{NaHCO}_3$ . The mixture was extracted with  $\text{AcOEt}$ . The organic layer was washed with brine, dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified by preparative silica gel chromatography  
25 with  $\text{CHCl}_3$  /  $\text{MeOH}$  (10:1) as an eluent. The amorphous substance was solidified with ethyl ether to give N-{4-{2-[4-(4,5-dihydro-1H-imidazol-2-ylamino)phenyl]ethyl}-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (17.9 mg) as an off-white amorphous solid.

30 mp. 139-140°C

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.08 (3H, s), 2.71-2.87 (4H, m), 3.18 (3H, s), 3.25-3.41 (4H, m), 4.03 (2H, s), 6.95 (4H, s), 7.32 (2H, d,  $J=8.5\text{Hz}$ ), 7.82 (2H, d,  $J=8.5\text{Hz}$ ).

MS: 498 (M+H)<sup>+</sup>

**Production Example 56:** Synthesis of N-{4-[2-[4-(ethanimidoethylamino)phenyl]ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

5 N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (200 mg), methyl ethanimidothioate hydroiodide (202 mg) and MeOH (4 ml) were combined under N<sub>2</sub> atmosphere. The reaction mixture was refluxed for 3 hours. After cooled to room temperature, the  
10 mixture was concentrated *in vacuo*. The residue was purified by preparative NH silica gel chromatography with CHCl<sub>3</sub> / MeOH (10:1) as an eluent. The amorphous substance was solidified with ethyl ether to give N-{4-[2-[4-(ethanimidoethylamino)phenyl]ethyl]-5-[4-(methylsulfonyl)benzyl]-  
15 1,3-thiazol-2-yl}acetamide (102.4 mg) as a pale yellow amorphous solid.

mp. 81.5-83°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.83(3H, brs), 2.08(3H, s), 2.81(4H, m), 3.18(3H, s), 4.02(2H, s), 6.64(2H, brd, J=8.5Hz), 6.99(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.83(2H, d, J=8.5Hz),  
20 12.03(1H, brs).

MS: 471 (M+H)<sup>+</sup>

**Production Example 57:** Synthesis of N-[4-(2-[4-[(iminomethyl)amino]phenyl]ethyl)-1,3-thiazol-2-yl]acetamide

25 N-{4-[2-(4-Aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (150 mg) was dissolved in THF (2 ml) and pH=7 buffer (2 ml). Then, ethyl imidoformate hydrochloride (1.26 g) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 2 hours, and concentrated *in vacuo*. The residue was  
30 purified by flash column chromatography over silica gel with CH<sub>3</sub>CN / water (7:3) as an eluent. The oil was purified again by preparative silica gel chromatography with CHCl<sub>3</sub> / MeOH (5:1) as an eluent to give N-[4-(2-[4-

[(iminomethyl)amino]phenyl]ethyl)-1,3-thiazol-2-yl]acetamide (110 mg) as pale brown oil.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12 (3H, s), 2.81-3.01 (4H, m), 6.71 (1H, s), 7.09-8.00 (7H, m), 12.07 (1H, s).

5 MS: 289 (M+H)<sup>+</sup>

**Production Example 58:** Synthesis of N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl]acetamide

A mixture of methyl N-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)imidothiocarbamate hydroiodide (100 mg), hydrazine monohydrate (0.0525 ml) and THF (3 ml) was stirred at r.t. for 95 hours. The precipitate was filtered off. The filtrate was concentrated in vacuo. The residue was purified by preparative silica gel chromatography with CHCl<sub>3</sub> / MeOH (10:1) as an eluent to give N-{4-[2-(4-{[hydrazino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-yl]acetamide (62.7 mg) as a pale pink solid.

mp: 216.5-218°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12 (3H, s), 2.92 (4H, m), 6.75 (1H, s), 7.12 (2H, d, J=8.5Hz), 7.27 (2H, d, J=8.5Hz), 8.88 (1H, brs), 12.07 (1H, brs).

MS: 319 (M+H)<sup>+</sup>

**Production Example 59:** Synthesis of N-(4-{2-[4-(2-amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

25 Step 1

N-(4-{2-[4-(Chloromethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide was prepared from N-(4-{2-[4-(hydroxymethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide in a similar manner according to Step 5 of Production Example 53.

30 mp. 145-146°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.82-2.99 (4H, m), 4.72 (2H, s), 6.73 (1H, s), 7.20 (2H, d, J=8.0Hz), 7.33 (2H, d, J=8.0Hz), 12.08 (1H, brs).

MS: 295 (M+H)<sup>+</sup>Step 2

NaCN (115 mg), KI (130 mg) and water (1.8 ml) were combined, and then a solution of N-(4-{2-[4-(chloromethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (230 mg) in DMF (7 ml) was added dropwise to the mixture at 0°C. The reaction mixture was stirred at r.t. for 19 hours, poured into water, and extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated in vacuo. The residual solid was washed with ethyl ether to give N-(4-{2-[4-(cyanomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (149.1 mg) as a colorless solid.

mp. 160-161°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.82-2.97 (4H, m), 3.97 (2H, s), 6.73 (1H, s), 7.21 (2H, d, J=8.5Hz), 7.25 (2H, d, J=8.5Hz), 12.08 (1H, brs).

MS: 286 (M+H)<sup>+</sup>Step 3

N-(4-{2-[4-(Cyanomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (600 mg) was dissolved in MeOH (5 ml) and CHCl<sub>3</sub> (5 ml), and then HCl gas was bubbled at 0°C for 5 minutes with stirring. The reaction mixture was stood for 17 hours, and concentrated in vacuo. The residual solid was washed with ethyl ether to give methyl 2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethanimidoate hydrochloride (632.5 mg) as an off-white solid.

mp. 77-78°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12 (3H, s), 2.88 (4H, s), 4.92 (6H, brs), 6.75 (1H, s), 7.10-7.20 (4H, m), 12.11 (1H, brs).

MS: 318 (M+H)<sup>+</sup> freeStep 4

Methyl 2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethanimidoate hydrochloride (600 mg) was

dissolved in EtOH (12 ml). Then ammonium chloride (136 mg) and ammonia in methanol (2 ml) were added to the solution. The reaction mixture was refluxed for 4 hours under N<sub>2</sub> atmosphere. After cooled to r.t., the suspension was filtered *in vacuo*.

5 The filtrate was concentrated *in vacuo*, and the residue was solidified with EtOH / diethyl ether to give N-(4-{2-[4-(2-amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (338.6 mg) as an off-white solid.

mp. 190.5-192°C

10 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12 (3H, s), 2.89 (4H, m), 3.68 (2H, s), 6.74 (1H, s), 7.20 (2H, d, J=8.0Hz), 7.39 (2H, d, J=8.0Hz). MS: 303 (M+H)<sup>+</sup> free

#### Step 5

N-(4-{2-[4-(2-Amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (67 mg) was dissolved in 15 water (1 ml) and CH<sub>3</sub>CN (1 ml). The solution was made basic (pH=8) with saturated NaHCO<sub>3</sub>, and concentrated *in vacuo*. The residue was purified by preparative NH silica gel chromatography with CH<sub>3</sub>CN / water (7:3) as an eluent to give N- 20 (4-{2-[4-(2-amino-2-iminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (26 mg) as an off-white amorphous substance.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 2.89 (4H, m), 3.59 (2H, s), 6.72 (1H, s), 7.20 (2H, d, J=8.0Hz), 7.30 (2H, d, J=8.0Hz), 9.38 (3H, brs).

25 MS: 303 (M+H)<sup>+</sup>

Production Example 60: Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl)acetamide

#### Step 1

30 A mixture of N-{5-[4-(methylthio)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-[4-(methylthio)benzyl]-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z : E = 2 : 1) (570 mg) was dissolved

in CH<sub>2</sub>Cl<sub>2</sub> (6 ml) under N<sub>2</sub> atmosphere. Then *m*-CPBA (254 mg) was added portionwise to the solution at 0°C. The reaction mixture was stirred at r.t. for 1.5 hours, and diluted in MeOH / CHCl<sub>3</sub>. The organic solution was washed with 1N-Na<sub>2</sub>CO<sub>3</sub>, water and  
5 brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give a mixture of N-{5-[4-(methylsulfinyl)benzyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-[4-(methylsulfinyl)benzyl]-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z : E = 2 : 1) (282.8 mg) as a yellow  
10 amorphous substance.

Z : E = 2 : 1

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08 (3Hx2/3, s), 2.13 (3Hx1/3, s), 2.71 (3H, s), 4.18 (2Hx2/3, s), 4.44 (2Hx1/3, s), 6.73 (1Hx2/3, d, J=12.5Hz), 6.87 (1Hx2/3, d, J=12.5Hz), 7.34 (1Hx1/3, d, J=15.5Hz), 7.41-8.17 (7/3H, m), 7.41 (2Hx2/3, d, J=8.0Hz), 7.50 (2Hx1/3, d, J=8.0Hz), 7.63 (2Hx2/3, d, J=8.0Hz), 7.93 (2Hx1/3, d, J=8.0Hz), 8.14 (2Hx2/3, d, J=8.0Hz), 8.22 (2Hx1/3, d, J=8.0Hz), 11.89 (1Hx2/3, s), 12.20 (1Hx1/3, s).  
MS: 442 (M+H)<sup>+</sup>

## 20 Step 2

N-{4-[2-(4-Aminophenyl)ethyl]-5-[4-(methylsulfinyl)benzyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 6 of Production Example 45.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08 (3H, s), 2.62-2.84 (4H, m), 2.70 (3H, s), 3.94 (2H, s), 4.85 (2H, s), 6.46 (2H, d, J=8.5Hz), 6.77 (2H, d, J=8.5Hz), 7.23 (2H, d, J=8.5Hz), 7.58 (2H, d, J=8.5Hz), 12.00 (1H, s).  
MS: 414 (M+H)<sup>+</sup>

## 30 Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfinyl)benzyl]-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene)biscarbamate was prepared in

a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.08(3H, s), 2.69(3H, s), 2.86(4H, s), 3.98(2H, s), 7.12(2H, d, J=8.5Hz), 7.26(2H, d, J=8.0Hz), 7.43(2H, d, J=8.5Hz), 7.57(2H, d, J=8.0Hz), 9.95(1H, s), 11.43(1H, s), 12.02(1H, s).

MS: 656(M+H)<sup>+</sup>

#### Step 4

The title compound was prepared in a similar manner according to Step 2 of Production Example 48.

mp. 159.5-161°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.07(3H, s), 2.44(3H, s), 2.79(4H, s), 3.86(2H, s), 6.78(2H, d, J=8.5Hz), 7.02(2H, d, J=8.5Hz), 7.04(2H, d, J=8.5Hz), 7.30(2H, d, J=8.5Hz).

MS: 440(M+H)<sup>+</sup>

**Production Example 61:** Synthesis of N-{4-[4-(3-{[amino(imino)methyl]amino}propyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

#### Step 1

To a solution of methyl 4-{[4-(methylthio)phenyl]acetyl}benzoate (5 g) in dichloromethane (250 ml) were added acetic acid (0.65 ml) and pyridinium bromide perbromide (6.51 g) at 0°C, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was poured into water (250 ml) and extracted with ethyl acetate (250 ml). The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated. The residue was washed with diisopropylethyl ether and collected by filtration to give methyl 4-{2-bromo[4-(methylthio)phenyl]acetyl}benzoate as an off-white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.47(3H, s), 3.94(3H, s), 6.33(3H, s), 7.23(2H, d, J=8.5Hz), 7.43(2H, d, J=8.5Hz).

#### Step 2

Methyl 4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}benzoate was prepared in a similar manner according to Step 2 of Production Example 46.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.47(3H, s), 3.83(3H, s), 7.08-  
5 7.32(4H, m), 7.52(2H, d, J=8.5Hz), 7.85(2H, d, J=8.5Hz).

MS: 357.1(M+H)<sup>+</sup>

### Step 3

To a solution of methyl 4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}benzoate (100 mg) in  
10 tetrahydrofuran (4 ml) was added portionwise lithium aluminium hydride (21.3 mg), and the mixture was stirred for 1 h at 20°C. To the reaction mixture were added ethyl acetate (10 ml) and water (3 ml). The resulting precipitate was removed by  
filtration, and the filtrate was washed with brine, dried over  
15 sodium sulfate and evaporated to give (4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}phenyl)methanol as a yellow solid, that was used as crude in the next reaction.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.46(3H, s), 4.46(2H, d, J=6.0Hz),  
5.17(t, 1H, J=5.5Hz), 7.13(d, 2H, J=5.5Hz), 7.17(d, 2H,  
20 J=5.5Hz), 7.20(d, 2H, J=8.5Hz), 7.34(d, 2H, J=8.5Hz).

MS: 329.2(M+H)<sup>+</sup>

### Step 4

To a suspension of (4-{2-amino-5-[4-(methylthio)phenyl]-1,3-thiazol-4-yl}phenyl)methanol (89.3 mg) in dichloromethane  
25 (1 ml) were added pyridine (0.11 ml) and acetylchloride (42.5 μl) at 0°C, and the mixture was stirred at the same temperature for 1 hr. To the reaction mixture was added 1N-hydrochloric acid (10 ml), and the mixture was extracted with ethyl acetate (20 ml x 2). The organic layer was washed with water and  
30 brine, dried over magnesium sulfate and evaporated to give a crude green solid (77.6 mg). To a solution of the crude green solid in dichloromethane (3 ml) was added 3-chloroperbenzoic acid (80.7 mg) at 0°C, and the mixture was stirred for 2 hr at

20°C. To the reaction mixture was added saturated sodium hydrogencarbonate aqueous solution (10 ml), and the mixture was extracted with ethyl acetate (20 ml x 2), washed with water and brine, dried over magnesium sulfate, and evaporated  
5 to give 4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}benzyl acetate as a brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.77(3H, s), 2.14(3H, s), 3.10(3H, s), 5.12(2H, s), 7.32(2H, d, J=8.5Hz), 7.45(2H, d, J=8.5Hz), 7.52(2H, d, J=8.5Hz), 7.88(2H, d, J=8.5Hz), 11.1(1H, brs).

10 MS: 467.0(M+Na)<sup>+</sup>

#### Step 5

To a suspension of 4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}benzyl acetate (1.218 g) in methanol (24 ml) was added potassium carbonate (379 mg)  
15 at 20°C, and the mixture was stirred for 1 h. To the reaction mixture was added 0.1N-hydrochloric acid (27.4 ml), and the mixture was extracted with chloroform (500 ml), dried over magnesium sulfate and evaporated to give N-{4-[4-(hydroxymethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-  
20 thiazol-2-yl}acetamide as a yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.87(3H, s), 3.09(3H, s), 4.72(2H, s), 7.31(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz), 7.51(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 10.83(1H, brs).

MS: 425.0(M+Na)<sup>+</sup>

#### 25 Step 6

To a solution of N-{4-[4-(hydroxymethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (867.4 mg) in methanol (0.6 ml) and chloroform (10 ml) was added manganese(IV) oxide (6.65 g) at 20°C under N<sub>2</sub> atmosphere, and  
30 the mixture was stirred for 19 hrs. The reaction mixture was filtered through a celite pad. The filtrate was evaporated to give N-{4-(4-formylphenyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow solid, that was used as

crude in the next reaction.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.20 (3H, s), 3.26 (3H, s), 7.63 (2H, d, J=8.5Hz), 7.64 (2H, d, J=8.0Hz), 7.90 (2H, d, J=8.0Hz), 7.92 (2H, d, J=8.5Hz), 10.00 (1H, s), 12.5 (1H, brs).

<sup>5</sup> Step 7

To a suspension of N-{4-(4-formylphenyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (360 mg) in chloroform (7 ml) was added (carbethoxymethylene)triphenylphosphorane (626 mg) at 20°C, and the mixture was stirred for 1 h. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel (150 ml) with hexane / ethyl acetate (1:1-1:2) as an eluent to give ethyl (2E)-3-(4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}phenyl)acrylate as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.34 (3H, t, J=7.0Hz), 1.93 (3H, s), 3.10 (3H, s), 4.28 (2H, q, J=7.0Hz), 6.45 (1H, d, J=16.1Hz), 7.48 (4H, s), 7.54 (2H, d, J=8.5Hz), 7.67 (2H, d, J=16.1Hz), 7.89 (2H, d, J=8.5Hz), 10.39 (1H, s).

<sup>20</sup> MS: 493.1 (M+Na)+

Step 8

To a suspension of ethyl (2E)-3-(4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}phenyl)acrylate (306.5 mg) in tetrahydrofuran (3 ml) was added portionwise lithium borohydride (271 mg) at 0°C, and the mixture was stirred for 6.5 h at 20°C. The reaction mixture was poured into a mixture of saturated ammonium chloride aqueous solution (50 ml) and chloroform (50 ml) at 0°C. The organic layer was separated, dried over magnesium sulfate and evaporated to give a crude yellow solid (300 mg). The residue was purified by column chromatography over silica gel (80 ml) with hexane / ethyl acetate (1:2-1:5) as an eluent to give N-{4-[4-(3-hydroxypropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-

thiazol-2-yl}acetamide as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.71(3H, s), 1.80-1.99(2H, m), 2.61-2.82(2H, m), 3.09(3H, s), 3.69(2H, dd, J=6.0, 10.0Hz), 7.17(2H, d, J=8.0Hz), 7.37(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 11.1(1H, s).

MS: 431.20 (M+1)<sup>+</sup>

#### Step 9

To a solution of N-{4-[4-(3-hydroxypropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (75 mg) in tetrahydrofuran (0.7 ml) were added triphenylphosphine (68.5 mg) and carbon tetrabromide (86.7 mg) at 0°C, and the mixture was stirred for 1 h at 20°C. The reaction mixture was purified by preparative thin-layer chromatography over silica gel with hexane / ethyl acetate (1:2) as an eluent to give N-{4-[4-(3-bromopropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as colorless oil.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.67(3H, s), 2.08-2.28(2H, m), 2.80(2H, t, J=7.5Hz), 3.10(3H, s), 3.41(2H, t, J=6.5Hz), 7.18(2H, d, J=8.0Hz), 7.39(2H, d, J=8.0Hz), 7.53(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz), 11.1(1H, s).

MS: 515.0 (M+Na)<sup>+</sup>

#### Step 10

To a solution of N-{4-[4-(3-bromopropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (82 mg) in N,N-dimethylformamide (0.82 ml) was added phthalimide potassium salt (30.8 mg), and the mixture was stirred for 2hrs. at 50°C. The reaction mixture was cooled to 20°C, then water was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated to give a crude material (92.0 mg). The crude material was purified by preparative thin-layer chromatography over silica gel to give N-{4-[4-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]phenyl]-5-[4-

(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.72(3H, s), 1.90-2.13(2H, m), 2.60-2.79(2H, m), 3.09(3H, s), 3.74(2H, t, J=7.3Hz), 7.18(2H, d, J=8.0Hz), 7.37(2H, d, J=8.0Hz), 7.52(2H, d, J=8.5Hz), 7.66-7.78(2H, m), 7.80-7.92(4H, m), 11.0(1H, s).

MS: 582.1(M+Na)<sup>+</sup>

#### Step 11

To a solution of N-{4-[4-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (53.2 mg) in acetonitrile (0.5 ml) was added hydrazine monohydrate (46.1 μl), and the mixture was stirred at 50°C for 30 min. The volatiles were evaporated. To the mixture was added chloroform (1 ml), and an insoluble material was removed by filtration. The filtrate was purified by preparative thin-layer chromatography over NH silica gel with chloroform / methanol (10:1) as an eluent to give N-{4-[4-(3-aminopropyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.69(3H, s), 1.69-1.88(2H, m), 2.60-2.74(2H, m), 2.76(2H, t, J=7.0Hz), 3.09(3H, s), 7.15(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz), 7.86(2H, d, J=8.5Hz).

MS: 428.2(M-H)<sup>-</sup>

#### Step 12

Di-tert-butyl ((E)-{[3-(4-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}phenyl)propyl]amino}methylenidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.50(9H, s), 1.87-1.97(2H, m), 2.01(3H, s), 2.69(2H, t, J=8.1Hz), 3.09(3H, s), 3.41-3.54(2H, m), 7.16(2H, d, J=8.1Hz), 7.36(2H, d, J=8.1Hz), 7.54(2H, d, J=8.5Hz), 7.87(2H, d, J=8.4Hz), 8.38(1H, t,

J=5.1Hz), 9.87(1H, brs), 11.5(1H, s).

MS: 694.2(M+Na)<sup>+</sup>

### Step 13

The title compound was prepared in a similar manner  
5 according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.72-1.85(2H, m), 2.19(3H, s), 2.58-  
2.66(2H, m), 3.08-3.18(2H, m), 3.25(3H, s), 6.65-7.58(4H,  
brs), 7.21(2H, d, J=8.4Hz), 7.36(2H, d, J=8.1Hz), 7.56(2H, d,  
J=8.4Hz), 7.67(1H, t, J=5.1Hz), 7.89(2H, d, J=8.4Hz), 12.4(1H,  
10 s).

MS: 472.1(M+H)<sup>+</sup> free

**Production Example 62:** Synthesis of N-{4-(2-{4-  
[(aminooxy)methyl]phenyl}ethyl)-5-[4-(methylsulfonyl)phenyl]-  
1,3-thiazol-2-yl}acetamide

### 15 Step 1

Methyl 4-((E)-2-{2-(acetylamino)-5-[4-  
(methylthio)phenyl]-1,3-thiazol-4-yl}vinyl)benzoate was  
prepared from N-{5-[4-(methylthio)phenyl]-4-formyl-1,3-  
thiazol-2-yl}acetamide in a similar manner according to Step 1  
20 of Production Example 53.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12(3Hx1/3, s), 2.19(3Hx2/3, s),  
2.54(3H, s), 3.85(3H, s), 6.55(1Hx1/3, d, J=12.6Hz),  
6.73(1Hx1/3, d, J=12.6Hz), 7.17-7.72(8H+2Hx2/3, m),  
7.84(2Hx1/3, d, J=8.5Hz), 7.93(2Hx2/3, d, J=8.5Hz), 12.31(1H,  
25 brs).

MS: 423.1(M-H)<sup>-</sup>

### Step 2

Methyl 4-((E)-2-{2-(acetylamino)-5-[4-  
(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}vinyl)benzoate was  
30 prepared in a similar manner according to Step 2 of Production  
Example 32.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15(3Hx1/5, s), 2.21(3Hx4/5, s),  
3.24(3Hx1/5, s), 3.30(3Hx4/5, s), 3.84(3Hx1/5, s),

3.85 (3Hx4/5, s), 6.64 (1Hx1/5, d, J=12.6Hz), 6.81 (1Hx1/5, d, J=12.6Hz), 7.31 (1Hx4/5, d, J=15.6Hz), 7.52 (1Hx4/5, d, J=15.6Hz), 7.30-8.11 (8H, m), 12.24 (1Hx1/5, s), 12.49 (1Hx4/5, s).

5 MS: 479.0 (M+Na)<sup>+</sup>

Step 3

Methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}ethyl)benzoate was prepared in a similar manner according to Step 6 of Production

10 Example 45.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.31 (3H, s), 2.97-3.07 (4H, m), 3.08 (3H, s), 3.91 (3H, s), 7.09 (2H, d, J=8.1Hz), 7.32 (2H, d, J=8.1Hz), 7.87 (4H, d, J=8.1Hz), 8.75 (1H, s).

MS: 481.0 (M+Na)<sup>+</sup>

15 Step 4

N-{4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 4 of Production Example 53.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17 (3H, s), 2.96 (4H, s), 3.24 (3H, s), 4.43 (2H, s), 7.06 (2H, d, J=8.1Hz), 7.18 (2H, d, J=8.1Hz), 7.50 (2H, d, J=8.4Hz), 7.91 (2H, d, J=8.4Hz), 12.33 (1H, s).

MS: 453.1 (M+Na)<sup>+</sup>

Step 5

25 N-{4-{2-[4-(Hydroxymethyl)phenyl]ethyl}-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (100 mg), N-hydroxyphthalimide (39.8 mg), triphenylphosphine (64 mg) and tetrahydrofuran (2 ml) were combined under nitrogen atmosphere, then, diethyl azodicarboxylate (40 wt% solution in  
30 toluene) (0.111 ml) was added to the solution at 0°C, and the mixture was stirred at 20°C for 5 hrs. The reaction mixture was poured into saturated sodium hydrogen carbonate aqueous solution, and extracted with chloroform. The organic layer was

washed with brine, dried over magnesium sulfate, filtered and evaporated. The crude material was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (30:1) as an eluent to give N-{4-[2-(4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl)phenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide as a yellow foam.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.30 (3H, s), 2.95-3.00 (4H, m), 3.09 (3H, s), 5.15 (2H, s), 7.04 (2H, d, J=8.1Hz), 7.21-7.92 (10H, m), 9.31 (1H, brs).

MS: 598.1 (M+Na)<sup>+</sup>, 574.0 (M-H)<sup>-</sup>

#### Step 6

To a solution of N-{4-[2-(4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl)phenyl)ethyl]-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (116.8 mg) in N,N-dimethylformamide (1.1 ml) was added methylhydrazine (11.9 μl) under N<sub>2</sub> atmosphere, and the mixture was stirred at 20°C for 4hrs. The reaction mixture was concentrated *in vacuo*. Ethyl acetate was added to the residue, and the precipitate was filtered off. The filtrate was concentrated *in vacuo* to give a crude yellow solid (105.1 mg). The crude material was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (30:1) as an eluent to give a pale yellow powder. The obtained powder was washed with acetonitrile, and the precipitate was collected by filtration to give N-{4-(2-{4-[(aminooxy)methyl]phenyl)ethyl)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (8.4 mg) as a white solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.17 (3H, s), 2.91-3.02 (4H, m), 3.24 (3H, s), 4.51 (2H, s), 5.98 (2H, s), 7.09 (2H, d, J=8.1Hz), 7.19 (2H, d, J=8.1Hz), 7.51 (2H, d, J=8.4Hz), 7.91 (2H, d, J=8.1Hz), 12.33 (1H, brs).

MS: 468.0 (M+H)<sup>+</sup>

**Production Example 63:** Synthesis of N-{4-{2-[4-  
({[amino(imino)methyl]amino}methyl)phenyl]ethyl}-5-[4-  
(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide  
hydrochloride

<sup>5</sup> Step 1

N-{4-{2-[4-(Bromomethyl)phenyl]ethyl}-5-[4-  
(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide was  
prepared from N-(4-[2-{4-(hydroxymethyl)phenyl}ethyl]-5-[4-  
(methylsulfonyl)phenyl]-1,3-thiazol-2-yl)acetamide in a  
<sup>10</sup> similar manner according to Step 9 of Production Example 61.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>),  $\delta$  (ppm): 2.17 (3H, s), 2.90-3.10 (4H, m),  
3.23 (3H, s), 4.67 (2H, s), 7.10 (2H, d, J=8.1Hz), 7.31 (2H, d,  
J=8.1Hz), 7.48 (2H, d, J=8.4Hz), 7.90 (2H, d, J=8.4Hz),  
12.33 (21H, s).

<sup>15</sup> MS: 491.0 (M-H)<sup>-</sup>

Step 2

To a solution of N-{4-{2-[4-(bromomethyl)phenyl]ethyl}-5-  
[4-(methylsulfonyl)phenyl]-1,3-thiazol-2-yl}acetamide (70 mg)  
in N,N-dimethylformamide (1 ml) was added diformimide sodium  
<sup>20</sup> salt (13.5 mg), and the mixture was stirred for 10 min at 20°C.  
To the reaction mixture was added water, the mixture was  
extracted with ethyl acetate, washed with water twice, dried  
over magnesium sulfate, and evaporated to give a crude  
diformimide compound. The diformimide compound was suspended  
<sup>25</sup> in conc. hydrochloric acid (200  $\mu$ l), ethanol (2 ml) and methanol  
(0.5 ml). The reaction mixture was stirred at 20°C for 3hrs.,  
then at 50°C for 3hrs. The volatiles were evaporated. To the  
residue was added saturated sodium hydrogen carbonate aqueous  
solution, the mixture was extracted with chloroform, dried  
<sup>30</sup> over maganesium sulfate and evaporated to give crude N-{4-(2-  
{4-[aminomethyl]phenyl}ethyl)-5-[4-(methylsulfonyl)phenyl]-  
1,3-thiazol-2-yl}acetamide, that was used as crude in the next  
reaction.

MS: 428.8 (M+H)<sup>+</sup>

Step 3

Di-tert-butyl ((E)-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}ethyl)benzyl]amino}methylenidene)biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31. <sup>5</sup>  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.48 (9H, s), 1.51 (9H, s), 2.30 (3H, s), 2.98 (4H, s), 3.08 (3H, s), 4.57 (2H, d, J=5.1Hz), 7.04 (2H, d, J=8.1Hz), 7.17 (2H, d, J=8.1Hz), 7.38 (2H, d, J=8.4Hz), 7.91 (2H, d, J=8.4Hz), 8.54 (1H, t, J=5.1Hz), 8.79 (1H, s), 11.53 (1H, s). <sup>10</sup>  
MS: 672.2 (M+H)<sup>+</sup>

Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.  
<sup>15</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18 (3H, s), 2.90-3.05 (4H, m), 3.25 (3H, s), 4.31 (2H, d, J=6.2Hz), 6.65-7.73 (4H, brs), 7.14 (2H, d, J=8.1Hz), 7.18 (2H, d, J=8.1Hz), 7.52 (2H, d, J=8.4Hz), 7.93 (2H, d, J=8.4Hz), 12.35 (1H, s).  
MS: 506.0 (M-H)<sup>-</sup>

<sup>20</sup> Production Example 64: Synthesis of methyl 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}benzoate hydrochloride

Step 1

<sup>25</sup> Ethyl 4-(4-iodophenyl)-2-oxobutanoate was prepared from Ethyl 3-(4-iodophenyl)propanoate in a similar manner according to Step 2 of Production Example 47.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.35 (3H, t, J=7.0Hz), 2.90 (2H, t, J=7.5Hz), 3.15 (2H, t, J=7.5Hz), 4.31 (2H, q, J=7.0Hz), 6.96 (2H, d, J=8.0Hz), 7.61 (8.5Hz). <sup>30</sup>  
MS: 331.0 (M-H)<sup>-</sup>

Step 2

Ethyl 3-bromo-4-(4-iodophenyl)-2-oxobutanoate was

prepared in a similar manner according to Step 1 of Production Example 46.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.38 (3H, t, J=7.0Hz), 3.19 (1H, dd, J=7.5, 14.6Hz), 3.47 (1H, dd, J=7.5, 14.6Hz), 4.36 (2H, q, J=7.0Hz), 5.21 (1H, dd, J=7.5, 7.5Hz), 7.00 (2H, d, J=8.5Hz), 7.65 (2H, d, J=8.5Hz).

MS: 369.2

### Step 3

Ethyl 3-bromo-4-(4-iodophenyl)-2-oxobutanoate (1.32 g) was dissolved in ethanol (26 ml), and then, thiourea (244 mg) was added to the solution. The reaction mixture was refluxed for 1 h under nitrogen atmosphere. The cooled reaction mixture was evaporated *in vacuo*. The crude material was triturated with diethyl ether to give ethyl 2-amino-5-(4-iodobenzyl)-1,3-thiazole-4-carboxylate hydrobromide as a pale yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.27 (3H, t, J=7.0Hz), 4.28 (2H, q, J=7.0Hz), 4.31 (2H, s), 7.10 (2H, d, J=8.5Hz), 7.69 (2H, d, J=8.5Hz).

MS: 389.0 (M+H)<sup>+</sup>, 411.0 (M+Na)<sup>+</sup>

### Step 4

Ethyl 2-amino-5-(4-iodobenzyl)-1,3-thiazole-4-carboxylate hydrobromide (1.386 g) was dissolved in dichloromethane (14 ml) under nitrogen atmosphere. Then, pyridine (0.765 ml) and acetyl chloride (0.336 ml) were added dropwise to the solution at 0°C. The reaction mixture was stirred at 20°C for 1 h. The organic solution was washed with 1N-hydrochloric acid, water and brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was washed with diisopropyl ether to give ethyl 2-(acetylamino)-5-(4-iodobenzyl)-1,3-thiazole-4-carboxylate as a white solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.27 (3H, t, J=7.0Hz), 2.09 (3H, s), 4.26 (2H, q, J=7.0Hz), 4.43 (2H, s), 7.10 (2H, d, J=8.0Hz), 7.67 (2H, d, J=8.0Hz), 12.44 (1H, s).

MS: 431.0 (M+H)<sup>+</sup>, 453.0 (M+Na)<sup>+</sup>

Step 5

N-[4-Formyl-5-(4-iodobenzyl)-1,3-thiazol-2-yl]acetamide was prepared in a similar manner according to Step 4 of  
5 Production Example 46.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.11 (3H, s), 4.48 (2H, s), 7.11 (2H, d, J=8.5Hz), 7.68 (2H, d, J=8.5Hz), 10.00 (1H, s).

MS: 409.0 (M+Na)<sup>+</sup>

Step 6

10 N-{5-(4-Iodobenzyl)-4-[2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner according to Step 5 of Production Example 45.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.07 (3Hx2/3, s), 2.15 (3Hx1/3, s), 3.96 (2Hx2/3, s), 4.12 (2Hx1/3, s), 6.63 (1Hx2/3, d, J=12.6Hz),  
15 6.70 (1Hx2/3, d, J=12.6Hz), 6.94 (2Hx2/3, d, J=8.0Hz), 6.99 (2Hx1/3, d, J=8.0Hz), 7.12 (1Hx1/3, d, J=15.6Hz), 7.25 (1Hx1/3, d, J=15.6Hz), 7.39 (2Hx2/3, d, J=9.0Hz), 7.56 (2Hx1/3, d, J=8.5Hz), 7.62 (2Hx2/3, d, J=8.0Hz), 7.65 (2Hx1/3, d, J=8.5Hz), 8.00 (2Hx2/3, d, J=8.5Hz),  
20 8.22 (2Hx1/3, d, J=8.5Hz), 9.85 (1Hx1/3, s), 10.18 (1Hx2/3, s).

MS: 528.0 (M+H)<sup>+</sup>

Step 7

To a solution of a mixture of N-{5-(4-iodobenzyl)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-  
25 (4-iodobenzyl)-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z:E=2:1) (558.2 mg) in methanol (2.8 ml) and N,N-dimethylformamide (5.5 ml) were added palladium(II) acetate (49.6 mg), 1,3-bis(diphenylphosphino)propane (109 mg) and triethylamine (308 μl). Carbon monoxide gas was bubbled  
30 through the solution for 30 min at 25°C. Then the reaction mixture was stirred for 6 hrs. at 70°C under carbon monoxide atmosphere. The reaction mixture was cooled to 25°C, diluted with ethyl acetate, washed with brine, dried over magnesium

sulfate and evaporated to give a crude yellow foam (645 mg). The crude foam was purified by flash column chromatography over silica gel with toluene / ethyl acetate (2:1-3:2) as an eluent, and triturated with ethyl ether to give a mixture of  
5 N-{5-(4-(methoxycarbonyl)benzyl)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide and N-{5-(4-(methoxycarbonyl)benzyl)-4-[(E)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (Z:E=2:3) as a yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.09(3Hx2/5, s), 2.20(3Hx3/5, s),  
10 3.91(3H, s), 4.10(2Hx2/5, s), 4.25(2Hx3/5, s), 7.27(2Hx2/5, s), 7.14(1Hx3/5, d, J=15.6Hz), 7.25(2Hx2/5, d, J=9.0Hz), 7.29(1Hx3/5, d, J=15.6Hz), 7.31(2Hx3/5, d, J=8.5Hz), 7.38(2Hx2/5, d, J=9.0Hz), 7.57(2Hx3/5, d, J=8.5Hz), 7.97(2Hx2/5, d, J=8.5Hz), 7.99(2Hx2/5, d, J=9.0Hz),  
15 8.00(2Hx3/5, d, J=8.5Hz), 8.20(2Hx3/5, d, J=9.0Hz), 9.55(1Hx3/5, brs), 10.11(1Hx2/5, brs).

MS: 460.1 (M+Na)<sup>+</sup>

#### Step 8

Methyl 4-((2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-  
20 1,3-thiazol-5-yl)methyl)benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.20(3H, s), 2.80(4H, s), 3.40-  
3.67(2H, m), 3.83(2H, s), 3.90(3H, s), 6.57(2H, d, J=8.5Hz),  
6.84(2H, d, J=8.5Hz), 7.09(2H, d, J=8.0Hz), 7.91(2H, d,  
25 J=8.5Hz), 8.96(1H, brs).

MS: 410.2 (M+H)<sup>+</sup>, 432.2 (M+Na)<sup>+</sup>

#### Step 9

Methyl 4-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-  
30 butoxycarbonyl)imino]methyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl)methyl]benzoate was prepared in a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.54(9H, s), 2.20(2H, s),

2.83(4H, s), 3.88(2H, s), 3.89(3H, s), 7.03(2H, d, J=8.5Hz), 7.17(2H, d, J=8.0Hz), 7.44(2H, d, J=8.0Hz), 7.93(2H, d, J=8.5Hz), 9.09(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 652.3(M+H)<sup>+</sup>, 652.3(M+Na)<sup>+</sup>

<sup>5</sup> Step 10

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.86(4H, s), 3.83(3H, s), 3.96-4.10(2H, m), 7.13(2H, d, J=8.5Hz), 7.24(2H, d, J=9.0Hz), 7.28(2H, d, J=8.5Hz), 7.35(4H, s), 7.89(2H, d, J=8.0Hz), 9.71(1H, s), 12.01(1H, s).

MS: 452.2(M+H)<sup>-</sup> free

Production Example 65: Synthesis of 4-([2-(acetylamino)-4-[2-(4-([amino(imino)methyl]amino)phenyl)ethyl]-1,3-thiazol-5-yl)methyl)-N,N-dimethylbenzamide hydrochloride

<sup>15</sup> Step 1

Methyl 4-([2-(acetylamino)-4-(2-[4-[(tert-butoxycarbonyl)amino]phenyl)ethyl]-1,3-thiazol-5-yl)methyl)benzoate was prepared from the compound obtained in Step 8 of Production Example 64 in a similar manner according to Step 1 of Production Example 52.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.52(9H, s), 2.23(3H, s), 2.81(4H, s), 3.86(2H, s), 3.90(3H, s), 6.93(2H, d, J=8.0Hz), 7.13(2H, d, J=8.5Hz), 7.19(2H, d, J=8.0Hz), 7.91(2H, d, J=8.5Hz), 8.48-9.69(1H, brs).

MS: 510.2(M+H)<sup>+</sup>, 532.3(M+Na)<sup>+</sup>

Step 2

Methyl 4-([2-(acetylamino)-4-(2-[4-[(tert-butoxycarbonyl)amino]phenyl)ethyl]-1,3-thiazol-5-yl)methyl)benzoate (287.7 mg), 1N-sodium hydroxide (1.41 ml) and ethanol (2.9 ml) were combined, and the mixture was refluxed for 3 hrs. After cooling to 25°C, the organic solvent was removed *in vacuo*. The aqueous solution was acidified with

1N-hydrochloric acid (pH=4), and the precipitate was filtered in *vacuo* to give 312.5 mg of a pale yellow solid. The solid was dissolved in pyridine (4.3 ml) under nitrogen atmosphere, and then, acethyl chloride (0.12 ml) was added dropwise to the solution at 0°C. The reaction mixture was stirred at 25°C for 3 hrs., and pyridine was removed in *vacuo*. The residue was suspended in water, and acidified with 1N-hydrochloric acid. The precipitate was collected in *vacuo*. The solid was washed with water and diethyl ether to give 4-([2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoic acid as a pale yellow solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.47(9H, s), 2.08(3H, s), 2.70-2.90(4H, m), 3.92(2H, s), 6.99(2H, d, J=8.4Hz), 7.10(2H, d, J=8.0Hz), 7.33(2H, d, J=8.0Hz), 7.81(2H, d, J=8.4Hz), 9.24(1H, s), 12.00(1H, s), 12.84(1H, brs).

MS: 494.4 (M-H)<sup>-</sup>

### Step 3

To a solution of 4-([2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]methyl}benzoic acid (50 mg) in 0.5 ml of dichloromethane were added methylamine hydrochloride (10.7 mg), 1-hydroxybenzotriazole (20.4 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (55.3 μl), then, the mixture was stirred for 3 hrs. at 25°C. The reaction mixture was diluted with 10 ml of chloroform and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under vacuum. The residue was triturated with ethyl acetate and diisopropylether, and collected by filtration to give tert-butyl {4-[2-(2-(acetylamino)-5-{4-[(dimethylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.51(9H, s), 2.23(3H, s), 2.83(4H, s), 2.95(3H, s), 3.09(3H, s), 3.82(2H, s), 6.47-6.81(1H, brs),

6.94 (2H, d, J=8.1Hz), 7.05 (2H, d, J=8.1Hz), 7.18 (2H, d, J=8.1Hz), 7.28 (2H, d, J=8.1Hz), 8.50-9.09 (1H, brs).

MS: 523.3 (M+H)<sup>+</sup>, 545.2 (M+Na)<sup>+</sup>

#### Step 4

5       tert-Butyl {4-[2-(2-(acetylamino)-5-{4-  
[(dimethylamino)carbonyl]benzyl)-1,3-thiazol-4-  
yl)ethyl]phenyl}carbamate (39.1 mg) and trifluoroacetic acid  
(1 ml) were combined at 0°C. The reaction mixture was stirred  
at 25°C for 2 hrs., and concentrated *in vacuo*. The residue was  
10 added to chloroform (20 ml) and 1N-sodium hydroxide (10 ml).  
The organic layer was separated, dried with magnesium  
sulfate, and evaporated to give yellow oil (33.3 mg). The  
crude yellow oil, N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-  
carboxamidine (45.8 mg) and tetrahydrofuran (0.5 ml) were  
15 combined under nitrogen atmosphere, and the mixture was  
stirred at 25°C for 34 hrs. To the reaction mixture was added  
N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (11  
mg), and the mixture was stirred at 50°C for 3 hrs. Then, the  
mixture was concentrated *in vacuo*. The residue was purified by  
20 preparative thin-layer chromatography over silica gel with  
chloroform / methanol (20:1) as an eluent to give di-tert-  
butyl [(E)-((4-[2-(2-(acetylamino)-5-{4-  
[(dimethylamino)carbonyl]benzyl)-1,3-thiazol-4-  
yl)ethyl]phenyl)amino)methylidene]biscarbamate as colorless  
25 oil (12.9 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.54 (9H, s), 2.21 (3H, s),  
2.85 (4H, s), 2.96 (3H, brs), 3.08 (3H, brs), 3.86 (2H, s),  
7.06 (2H, d, J=8.5Hz), 7.14 (2H, d, J=8.1Hz), 7.33 (2H, d,  
J=8.5Hz), 7.46 (2H, d, J=8.5Hz), 8.81-9.21 (1H, brs), 10.25 (1H,  
30 s), 11.63 (1H, s).

MS: 665.3 (M+H)<sup>+</sup>, 687.2 (M+Na)<sup>+</sup>

#### Step 5

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.86(4H, s), 2.88(3H, s), 2.96(3H, s), 3.97(2H, s), 7.12(2H, d, J=8.4Hz), 7.16(2H, d, J=8.1Hz), 7.23(2H, d, J=8.4Hz), 7.32(2H, d, J=8.1Hz),  
5 7.34(4H, s), 9.70(1H, s), 12.01(1H, s).

MS: 465.2 (M+H)<sup>+</sup> free

**Production Example 66:** Synthesis of 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-N-methylbenzamide hydrochloride

10 Step 1

tert-Butyl {4-[2-(2-(acetylamino)-5-{4-[(methylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from the compound obtained in Step 2 of Production Example 65 in a similar  
15 manner according to Step 3 of Production Example 65.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.52(9H, s), 2.23(3H, s), 2.78-2.89(4H, m), 3.00(3H, d, J=4.8Hz), 3.83(2H, s), 6.20(2H, d, J=4.8Hz), 6.36-6.78(1H, brs), 6.94(2H, d, J=8.4Hz), 7.05(2H, d, J=8.4Hz), 7.18(2H, d, J=8.4Hz), 7.63(2H, d, J=8.4Hz), 8.60-  
20 9.09(1H, brs).

MS: 509.2 (M+H)<sup>+</sup>, 531.2 (M+Na)<sup>+</sup>

Step 2

Di-tert-butyl [(E)-({4-[2-(2-(acetylamino)-5-{4-[(methylamino)carbonyl]benzyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.54(9H, s), 2.22(3H, s), 2.83(4H, s), 2.99(3H, d, J=4.8Hz), 3.86(2H, s), 6.16(1H, d, J=4.0Hz), 7.01(2H, d, J=8.4Hz), 7.13(2H, d, J=8.4Hz), 7.42(2H, d, J=8.4Hz), 7.66(2H, d, J=8.4Hz), 8.77-9.10(1H, brs),  
30 10.24(1H, s), 11.62(1H, s).

MS: 651.3 (M+H)<sup>+</sup>, 673.3 (M+Na)<sup>+</sup>

Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08 (3H, s), 2.76 (3H, d, J=4.8Hz), 2.86 (4H, s), 3.98 (2H, s), 7.13 (2H, d, J=8.4Hz), 7.19 (2H, d, J=8.1Hz), 7.23 (2H, d, J=8.4Hz), 7.30 (4H, s), 7.74 (2H, d, J=8.1Hz), 8.38 (2H, d, J=4.4Hz), 9.62 (1H, s), 11.99 (1H, s).

MS: 451.3 (M+H)<sup>+</sup> free

**Production Example 67:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(dimethylamino)methyl]-1,3-thiazol-2-yl}acetamide dihydrochloride

#### Step 1

To a solution of N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (500 mg) in acetic acid (3 ml) were added dimethylamine hydrochloride (169 mg) and paraformaldehyde (62.2 mg), and the mixture was stirred at 100°C (bath temp.) for 2 hrs. The solvent was removed in vacuo, and the mixture was adjusted to pH=9 with saturated sodium hydrogen carbonate aqueous solution, extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated. The crude compound was purified by flash column chromatography over silica gel with dichloromethane / methanol (100:1) → (20:1) as an eluent to give N-{5-[(dimethylamino)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide as a yellow amorphous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.08 (3H, s), 2.26 (6H, s), 3.47 (2H, s), 6.63 (1H, d, J=12.6Hz), 6.70 (1H, d, J=12.6Hz), 7.43 (2H, d, J=9.0Hz), 8.03 (2H, d, J=9.0Hz), 10.20 (1H, brs).

MS: 347 (M+H)<sup>+</sup>, 369 (M+Na)<sup>+</sup>

#### Step 2

N-{4-[2-(4-Aminophenyl)ethyl]-5-[(dimethylamino)methyl]-1,3-thiazol-2-yl}acetamide was prepared in a similar manner

according to Step 6 of Production Example 45.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.19(6H, s), 2.23(3H, s), 2.80(4H, s), 3.30(2H, s), 3.56(2H, s), 6.60(2H, d, J=8.4Hz), 6.91(2H, d, J=8.4Hz), 8.54-8.84(1H, brs).

<sup>5</sup> MS: 317.2 (M-H)<sup>-</sup>

### Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-  
[(dimethylamino)methyl]-1,3-thiazol-4-  
yl)ethyl)phenyl]amino}methylenidene)biscarbamate was prepared in  
<sup>10</sup> a similar manner according to Step 7 of Production Example 45.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.21(6H, s), 2.22(3H, s), 2.87(4H, s), 3.36(2H, s), 7.09(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 8.89-9.97(1H, brs), 10.24(1H, s), 11.63(1H, s).

<sup>15</sup> MS: 561.3 (M+H)<sup>+</sup>, 583.3 (M+Na)<sup>+</sup>

### Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.66(3H, s), 2.68(3H, s), 2.96(4H, s), 4.37(2H, d, J=4.8Hz), 7.15(2H, d, J=8.4Hz), 7.32(2H, d, J=8.4Hz), 7.51(4H, s), 10.08(1H, s), 10.64(1H, t, J=4.8Hz), 12.33(1H, s).

MS: 361.1 (M+H)<sup>+</sup>

**Production Example 68:** Synthesis of N-{5-[(4-acetyl-1-  
<sup>25</sup> piperazinyl)methyl]-4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-2-  
yl}acetamide dihydrochloride

### Step 1

N-{5-[(4-Acetyl-1-piperazinyl)methyl]-4-[(Z)-2-(4-  
<sup>30</sup> nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared  
from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-  
yl}acetamide in a similar manner according to Step 1 of  
Production Example 67.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.08 (6H, s), 2.34-2.59 (4H, m), 3.41-3.53 (2H, m), 3.56 (2H, s), 3.58-3.69 (2H, m), 6.62 (1H, d, J=12.6Hz), 6.68 (1H, d, J=12.6Hz), 7.45 (2H, d, J=8.5Hz), 8.05 (2H, d, J=9.0Hz), 10.18 (1H, s).

5 MS: 452.0 (M+Na)<sup>+</sup>

### Step 2

N-{5-[(4-Acetyl-1-piperazinyl)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (1080 mg), methanol (2 ml), tetrahydrofuran (2 ml), acetic acid (0.3 ml) and then 10% palladium on carbon (150 mg) were combined under nitrogen atmosphere. The mixture was stirred under 3 atm hydrogen for 3 hrs. at 25°C. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated in vacuo to give a crude material (192.3 mg). To the residue was added saturated sodium hydrogen carbonate aqueous solution, and the mixture was extracted with chloroform. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo to give a pink amorphous substance (124.7 mg). The pink amorphous substance (124.7 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamide (93.6 mg) and tetrahydrofuran (2 ml) were combined under nitrogen atmosphere. The reaction mixture was stirred at 25°C for 14 hrs., and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(4-acetyl-1-piperazinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate as colorless oil (121.1 mg).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.53 (9H, s), 2.06 (3H, s), 2.24 (3H, s), 2.20-2.32 (2H, m), 2.33-2.44 (2H, m), 2.74-2.96 (4H, m), 3.30-3.45 (4H, m), 3.52-3.65 (2H, m), 7.04 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz), 8.85-10.17 (1H, brs), 10.25 (1H, s),

11.63 (1H, s).

MS: 644.3 (M+H)<sup>+</sup>, 666.1 (M+H)<sup>+</sup>

### Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.03 (3H, s), 2.16 (3H, s), 2.75-3.15 (8H, m), 3.16-3.63 (4H, m), 4.40 (2H, s), 7.15 (2H, d, J=8.0Hz), 7.32 (2H, d, J=8.0Hz), 7.49 (4H, s), 10.07 (1H, s), 11.29 (1H, brs), 12.33 (1H, s)

MS: 444.2 (M+H)<sup>+</sup> free

**Production Example 69:** Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(methylsulfonyl)-1-piperazinyl]methyl}-1,3-thiazol-2-yl)acetamide dihydrochloride

### Step 1

N-{5-{[4-(Methylsulfonyl)-1-piperazinyl]methyl}-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.08 (3H, s), 2.54-2.66 (4H, m), 2.80 (3H, s), 3.19-3.34 (4H, m), 3.58 (2H, s), 6.61 (1H, d, J=12.1Hz), 6.69 (1H, d, J=12.1Hz), 7.45 (2H, d, J=8.5Hz), 8.04 (2H, d, J=8.5Hz), 10.09 (1H, s).

MS: 467.2 (M+H)<sup>+</sup>, 488.1 (M+Na)<sup>+</sup>

### Step 2

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(methylsulfonyl)-1-piperazinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.54 (9H, s), 2.23 (3H, s), 2.41-2.56 (4H, m), 2.76 (3H, s), 2.80-2.89 (4H, m), 3.12-3.27 (4H, m), 3.42 (2H, s), 7.05 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz),

8.57-9.61 (1H, brs), 10.25 (1H, s), 11.63 (1H, s).

MS: 680.3 (M+H)<sup>-</sup>, 702.2 (M+Na)<sup>-</sup>

### Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16 (3H, s), 2.97 (4H, s), 3.00 (3H, s), 3.05-3.28 (4H, m), 3.28-3.48 (2H, m), 3.59-3.81 (2H, m), 4.35-4.60 (2H, brs), 7.16 (2H, d, J=8.1Hz), 7.32 (2H, d, J=8.1Hz), 7.39 (4H, s), 9.84 (1H, s), 10.64-10.89 (1H, brs), 12.34 (1H, s).

MS: 480.1 (M+H)<sup>-</sup> free

**Production Example 70:** Synthesis of N-[4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-(4-thiomorpholinylmethyl)-1,3-thiazol-2-yl]acetamide dihydrochloride

### Step 1

N-[4-[(Z)-2-(4-Nitrophenyl)vinyl]-5-(4-thiomorpholinylmethyl)-1,3-thiazol-2-yl]acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.08 (3H, s), 2.57-2.86 (8H, m), 3.53 (2H, s), 6.62 (1H, d, J=12.6Hz), 6.68 (1H, d, J=12.6Hz), 7.43 (2H, d, J=9.0Hz), 8.0332 (2H, d, J=9.0Hz), 10.16 (1H, s). MS: 405.1 (M+H)<sup>+</sup>, 427.1 (M+Na)<sup>+</sup>

### Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(4-thiomorpholinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.53 (9H, s), 2.22 (3H, s), 2.63 (8H, s), 2.80-2.90 (4H, m), 3.39 (2H, s), 7.06 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz), 8.82-9.39 (1H, brs), 10.24 (1H,

s), 11.63(1H, s).

MS: 619.3(M+H)<sup>+</sup>, 641.2(M+Na)<sup>+</sup>

### Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.69-2.87(2H, m), 2.97(4H, s), 3.02-3.19(4H, m), 3.48-3.61(2H, m), 4.42(2H, s), 7.15(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.40(4H, s), 9.86(1H, s), 10.51-10.69(1H, brs), 12.34(1H, s).

MS: 419.2(M+H)<sup>-</sup> free

**Production Example 71:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[2-(dimethylamino)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

### Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[2-(dimethylamino)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.72, 2.85(3H, s), 2.89, 2.98(3H, s), 3.16(4H, m), 4.01(2H, m), 7.07(2H, d, J=8.2 Hz), 7.32(2H, d, J=8.2 Hz), 7.87-7.95(1H, m), 9.21(1H, s), 12.36(1H, s).

MS: 490(M+H)<sup>+</sup>

### Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[2-(dimethylamino)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride was prepared in a similar manner according to Step 2 of Production Example 31.

white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.85(3H, s), 2.86-2.98(5H, m), 3.22(2H, dd, J=8.9, 5.3 Hz), 4.01(2H, d,

J=5.3 Hz), 7.27(2H, d, J=8.5 Hz), 7.33(2H, d, J=8.5 Hz),  
7.94(1H, t, J=5.3 Hz), 10.15(2H, br), 12.38(1H, s).

MS: 390(M+H)<sup>+</sup> free

### Step 3

5 Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[2-(dimethylamino)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31. white powder

10 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.85(3H, s), 2.85-2.94(2H, m), 2.97(3H, s), 3.17-3.26(2H, m), 4.00-4.04(2H, m), 7.19(1H, d, J=8.0 Hz), 7.42(2H, d, J=8.0 Hz), 7.88(1H, t, J=5.4 Hz), 9.93(1H, s), 11.43(1H, s), 12.38 (1H, s).

15 MS: 632(M+H)<sup>+</sup>

### Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31. white powder

20 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.84(3H, s), 2.89-2.695(2H, m), 2.98(3H, s), 3.19-3.26(2H, m), 3.99(2H, m), 7.13(2H, d, J=8.0 Hz), 7.28(2H, d, J=8.0 Hz), 7.43(4H, br), 7.97(1H, br), 9.86(1H, s), 12.38(1H, s).

MS: 432(M+H)<sup>+</sup> free

25 **Production Example 72:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(dimethylamino)-3-oxopropyl]-1,3-thiazole-5-carboxamide hydrochloride

### Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[3-(dimethylamino)-3-oxopropyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of

## Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.14(3H, s),  
2.55(2H, m), 2.73-2.94(8H, m), 3.14(2H, dd, J=9.1, 6.1 Hz),  
3.37(2H, m), 7.05(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz),  
5 7.89(1H, m), 9.21(1H, s), 12.33(1H, s).

MS: 504(M+H)<sup>+</sup>

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-[3-(dimethylamino)-3-oxopropyl]-1,3-thiazole-5-carboxamide  
10 hydrochloride was prepared in a similar manner according to  
Step 2 of Production Example 31.

white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.57(2H, m),  
2.81(3H, s), 2.84-2.98(5H, m), 3.20(2H, dd, J=8.9, 5.4 Hz),  
15 3.36(2H, dd, J=12.8, 7.1 Hz), 7.26(2H, d, J=8.6 Hz), 7.32(2H,  
d, J=8.6 Hz), 7.95(1H, t, J=5.4 Hz), 10.04(2H, br), 12.35(1H,  
br).

MS: 403(M+H)<sup>+</sup> free

Step 3

20 Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(dimethylamino)-3-oxopropyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in  
a similar manner according to Step 3 of Production Example 31.  
white powder

25 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.50(9H, s),  
2.14(3H, s), 2.80(3H, s), 2.81-2.93(2H, m), 2.94(3H, s), 3.13-  
3.29(6H, m), 3.34-3.43(2H, m), 7.17(2H, d), 7.42(2H, d),  
7.89(1H, m), 9.93(1H, s), 11.43(1H, s), 12.34(1H, m).

MS: 646(M+H)<sup>+</sup>

30 Step 4

The title compound was prepared in a similar manner  
according to Step 4 of Production Example 31.  
white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.56(2H, m), 2.81(3H, s), 2.87-2.95(5H, m), 3.19(2H, m), 3.34(2H, m), 7.11-7.38(4H, m), 7.43(4H, s), 8.02(1H, m), 8.55(1H, br), 9.88(1H, br), 12.36(1H, s).

5 MS: 445(M+H)<sup>+</sup> free

Production Example 73: Synthesis of 2-(acetylamino)-N-[2-(acetylamino)ethyl]-4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazole-5-  
carboxamide hydrochloride

10 Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[2-(acetylamino)ethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-  
15 5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 1.79(3H, s), 2.14(3H, s), 2.84(2H, m), 3.16-3.22(6H, m), 7.06(2H, d, J=8.5 Hz), 7.33(2H, d, J=8.5 Hz), 7.99(2H, m), 9.21(1H, s),  
20 12.33(1H, s).

MS: 490(M+H)<sup>+</sup>

Step 2

2-(Acetylamino)-N-[2-(acetylamino)ethyl]-4-[2-(4-aminophenyl)ethyl]-1,3-thiazole-5-carboxamide hydrochloride  
25 was prepared in a similar manner according to Step 2 of Production Example 31.

white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.79(3H, s), 2.15(3H, s), 2.90-2.98(2H, dd, J=10.1, 6.6 Hz), 3.14-3.26(6H, m), 7.27(2H,  
30 d, J=8.9 Hz), 7.32(2H, d, J=8.9 Hz), 7.97-8.06(2H, m), 10.18(2H, br), 12.35(1H, s).

MS: 390(M+H)<sup>+</sup> free

Step 3

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[2-(acetylamino)ethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

5 white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 1.79(3H, s), 2.15(3H, s), 2.89(2H, m), 3.18(6H, m), 7.18(2H, d, J=8.0 Hz), 7.42(2H, d, J=8.0 Hz), 7.95(2H, m), 9.93(1H, s), 11.43(1H, s), 12.35(1H, s).

10 MS: 632(M+H)<sup>+</sup>

#### Step 4

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

white powder

15 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.79(9H, s), 2.16(9H, s), 2.91(2H, m), 3.10-3.25(6H, m), 7.14(2H, d, J=8.2 Hz), 7.27(2H, d, J=8.2 Hz), 7.42(4H, br), 7.97(1H, br), 8.08(1H, br), 9.83(1H, s), 12.36(1H, s).

MS: 432(M+H)<sup>+</sup> free

20 Production Example 74: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-{2-[(methylsulfonyl)amino]ethyl}-1,3-thiazole-5-carboxamide hydrochloride

#### Step 1

25 tert-Butyl [4-(2-{2-(acetylamino)-5-[(2-[(methylsulfonyl)amino]ethyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl)phenyl]carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carboxylic acid in a similar manner according to Step 1 of  
30 Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.79-2.89(5H, m), 3.05-3.32(6H, m), 7.04-7.14(3H, m), 7.33(2H, d, J=8.3 Hz), 8.01(1H, br), 9.20(1H, s), 12.35(1H, s).

MS: 526 (M+H)<sup>+</sup>

Step 2

2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-N-{2-  
[(methylsulfonyl)amino]ethyl}-1,3-thiazole-5-carboxamide  
5 hydrochloride was prepared in a similar manner according to  
Step 2 of Production Example 31.

white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.89(3H, s),  
2.89-3.27(8H, m), 7.12(1H, t, J=5.7 Hz), 7.24(2H, d, J=8.5  
10 Hz), 7.32(2H, d, J=8.5 Hz), 8.05(1H, t, J=5.4 Hz), 9.95(2H,  
br), 12.36(1H, s).

MS: 425 (M+H)<sup>+</sup> free

Step 3

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(2-  
15 [(methylsulfonyl)amino]ethyl)amino]carbonyl]-1,3-thiazol-4-  
yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared in  
a similar manner according to Step 3 of Production Example 31.  
white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s),  
20 2.15(3H, s), 2.80-2.97(5H, m), 3.00-3.14(2H, m), 3.15-3.30(4H,  
m), 7.11(1H, m), 7.17(2H, d, J=8.5 Hz), 7.42(2H, d, J=8.5 Hz),  
8.01(1H, m), 9.93(1H, s), 11.43(1H, s), 12.37(1H, s).

MS: 668 (M+H)<sup>+</sup>

Step 4

25 The title compound was prepared in a similar manner  
according to Step 4 of Production Example 31.

white powder

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.90-2.96(5H,  
m), 3.08(2H, m), 3.19-3.29(4H, q), 7.14(2H, d, J=8.3 Hz),  
30 7.28(2H, d, J=8.3 Hz), 7.43(4H, br), 8.07(1H, m), 9.87(1H, s),  
12.38(1H, s).

MS: 467 (M+H)<sup>+</sup> free

Production Example 75: Synthesis of 2-(acetylamino)-4-[2-(4-

{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(dimethylamino)-3-oxopropyl]-N-methyl-1,3-thiazole-5-carboxamide hydrochloride  
Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{{[3-(dimethylamino)-3-oxopropyl](methyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.50(9H, s), 2.14(3H, s), 2.56(2H, t, J=7.3 Hz), 2.78(3H, s), 2.84-2.88(6H, m), 2.93(3H, s), 3.47(3H, m), 7.12(2H, d, J=8.4 Hz), 7.40(2H, d, J=8.4 Hz), 9.92(1H, s), 11.43(1H, s), 12.34(1H, s).  
MS: 659(M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.50-2.60(6H, m), 2.79(3H, s), 2.87(3H, s), 2.94(3H, s), 3.39-3.64(2H, m), 7.09-7.26(4H, m), 7.46(4H, br), 9.96(1H, s), 12.35(1H, s).  
MS: 460(M+H)<sup>+</sup> free

Production Example 76: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-{3-[benzyl(methyl)amino]-3-oxopropyl}-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-{{[3-[benzyl(methyl)amino]-3-oxopropyl]amino}carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino)methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.83(9H, s), 1.50(9H, s),

1.98-2.15 (3H, m), 2.60-2.63 (2H, m), 2.80-2.90 (5H, m), 3.17-3.21 (2H, m), 3.42-3.47 (2H, m), 4.50-4.57 (2H, m), 7.12-7.43 (9H, m), 7.95 (1H, m), 9.93 (1H, s), 11.44 (1H, s), 12.4 (1H, s).

MS: 722 (M+H)<sup>+</sup>

5 Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16, 2.30 (3H, s), 2.64 (2H, m), 2.64 (2H, m), 2.80-2.90 (5H, m), 3.14-3.25 (2H, m), 3.43-  
10 3.47 (2H, m), 4.51-4.57 (2H, m), 7.08-7.42 (9H, m), 8.02-8.04 (1H, m), 9.83-9.87 (1H, m), 12.36 (1H, m).

MS: 522 (M+H)<sup>+</sup> free

Production Example 77: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-(dimethylamino)-  
15 4-oxobutyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(dimethylamino)-4-oxobutyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
20 from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39 (9H, s), 1.50 (9H, s), 1.68 (2H, tt, J=6.8 Hz), 2.14 (3H, s), 2.30 (2H, t, J=6.8 Hz),  
25 2.80 (3H, s), 2.82-2.95 (2H, m), 2.92 (3H, s), 3.10-3.28 (4H, m), 7.18 (2H, d, J=8.5 Hz), 7.39 (2H, d, J=8.5 Hz), 9.92 (1H, s), 11.43 (1H, br), 12.3 (1H, br).

MS: 682 (M+Na)<sup>+</sup>

Step 2

30 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.69 (2H, m), 2.16 (2H, s), 2.31 (2H, t, J=7.2 Hz), 2.81 (3H, s), 2.87-2.95 (2H, m), 2.93 (3H,

s), 3.16-3.24 (4H, m), 3.57 (3H, s), 7.11-7.44 (4H, m), 8.06-8.23 (1H, m), 9.83-9.92 (1H, m), 12.35 (1H, s).

MS: 460 (M+H)<sup>+</sup> free

**Production Example 78:** Synthesis of (2R)-1-({2-(acetylamino)-  
5 4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-  
5-yl}carbonyl)-N,N-dimethyl-2-pyrrolidinecarboxamide  
hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(2R)-2-  
10 [(dimethylamino)carbonyl]-1-pyrrolidinyl}carbonyl)-1,3-  
thiazol-4-yl]ethyl}phenyl)amino]methylidene)biscarbamate was  
prepared from the compound obtained in Step 2 of Production  
Example 34 in a similar manner according to Step 1 of  
Production Example 32.

15 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39 (9H, s), 1.50 (9H, s),  
1.60-1.93 (3H, m), 2.06-2.30 (1H, m), 2.14 (3H, s), 2.66-  
3.14 (10H, m), 3.20-3.50 (2H, m), 4.89 (1H, m), 7.16 (2H, d, J=8.0  
Hz), 7.41 (2H, d, J=8.0 Hz), 9.92 (1H, s), 11.41 (1H, s),  
12.34 (1H, s).

20 MS: 694 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner  
according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.60-2.00 (3H, m), 2.15,  
25 2.48 (3H, s x2), 2.65-3.50 (12H, m), 3.60-3.75 (2H, m), 7.09-  
7.17 (2H, d x2), 7.23-7.31 (2H, d x2), 7.47 (3H, br), 9.94 (1H,  
br), 12.35, 12.59 (1H, s x2).

MS: 472 (M+H)<sup>+</sup> free

**Production Example 79:** Synthesis of (2S)-1-({2-(acetylamino)-  
30 4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-  
5-yl}carbonyl)-N,N-dimethyl-2-pyrrolidinecarboxamide  
hydrochloride

Step 1

Di-tert-butyl ((Z)-[(4-{2-[2-(acetylamino)-5-((2S)-2-  
[(dimethylamino)carbonyl]-1-pyrrolidinyl)carbonyl)-1,3-  
thiazol-4-yl]ethyl}phenyl)amino]methylidene)biscarbamate was  
prepared from the compound obtained in Step 2 of Production

5 Example 34 in a similar manner according to Step 1 of  
Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(3H, s), 1.50(9H, s),  
1.60-1.94(H, m), 2.14(3H, s), 2.10-2.36(1H, m), 2.67-3.11(10H,  
m), 3.30-3.52(2H, m), 4.88(1H, m), 7.16(2H, d, J=8.0 Hz),  
10 7.41(2H, d, J=8.0 Hz), 9.92(1H, s), 11.41(1H, s), 12.34(1H,  
s).

MS: 694(M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner  
15 according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.60-2.00(3H, m), 2.15,  
2.48(3H, s x2), 2.65-3.50(12H, m), 3.60-3.75(2H, m), 7.09-  
7.17(2H, d x2), 7.23-7.31(2H, d x2), 7.47(3H, br), 9.94(1H,  
br), 12.35, 12.59(1H, s x2).

20 MS: 472(M+H)<sup>+</sup> free

**Production Example 80:** Synthesis of 2-(acetylamino)-4-[2-(4-  
[[amino(imino)methyl]amino]phenyl)ethyl]-N-[2-  
(methylsulfonyl)ethyl]-1,3-thiazole-5-carboxamide  
hydrochloride

#### 25 Step 1

Di-tert-butyl ((Z)-[(4-{2-[2-(acetylamino)-5-([2-  
(methylsulfonyl)ethyl]amino)carbonyl)-1,3-thiazol-4-  
yl]ethyl}phenyl)amino]methylidene)biscarbamate was prepared  
from the compound obtained in Step 2 of Production Example 34  
30 in a similar manner according to Step 1 of Production Example  
32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.57(9H, s),  
2.15(3H, s), 2.87(2H, dd, J=8.8, 6.5 Hz), 3.02(3H, s), 3.19-

3.28 (2H, dd, J=9.0, 5.5 Hz), 3.30-3.36 (2H, m), 3.59 (2H, dd, J=12.0, 6.0 Hz), 7.17 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.4 Hz), 8.17 (1H, s), 9.93 (1H, s), 11.44 (1H, s), 12.40 (1H, s).

MS: 675 (M+Na)<sup>+</sup>

<sup>5</sup> Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16 (3H, s), 2.88-2.96 (2H, m), 3.03 (3H, s), 3.20-3.30 (4H, m), 3.33-3.60 (2H, m), 7.12-  
<sup>10</sup> 7.18 (2H, m), 7.26-7.46 (2H, d), 7.46 (4H, br), 8.27 (1H, t), 9.94 (1H, s), 12.41 (1H, s).

MS: 453 (M+H)<sup>+</sup> free

Production Example 81: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-(4-  
<sup>15</sup> pyridinylmethyl)-1,3-thiazole-5-carboxamide dihydrochloride  
Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[(4-pyridinylmethyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared  
<sup>20</sup> from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.40-1.50 (18H, br), 2.15 (3H, s), 2.89 (2H, m), 3.22 (2H, m), 4.39 (2H, d, J=5.7 Hz), 7.09-  
<sup>25</sup> 7.18 (2H, m), 7.32-7.44 (3H, m), 7.66 (1H, m), 8.43-8.62 (3H, m), 9.94 (1H, s), 11.44 (1H, s), 12.40 (1H, s).

MS: 660 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner  
<sup>30</sup> according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.18 (3H, s), 2.92 (2H, m), 3.13-3.28 (2H, m), 4.63 (2H, m), 7.12 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.47 (4H, br), 7.93 (2H, d, J=6.3 Hz), 8.88 (3H,

m), 10.00(1H, s), 12.43(1H, s).

MS: 438(M+H)<sup>+</sup> free

**Production Example 82:** Synthesis of 2-(acetylamino)-4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-N-(3-

5 pyridinylmethyl)-1,3-thiazole-5-carboxamide dihydrochloride  
Step 1

Di-tert-butyl [(Z)-{4-[2-(2-(acetylamino)-5-{{(3-  
pyridinylmethyl)amino}carbonyl}-1,3-thiazol-4-  
yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared  
10 from the compound obtained in Step 2 of Production Example 34  
in a similar manner according to Step 1 of Production Example  
32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.50(9H, s),  
2.16(3H, s), 2.89(2H, dd, J=8.6, 6.7 Hz), 3.22(2H, dd, J=8.6,  
15 5.7 Hz), 4.38(2H, d, J=5.7 Hz), 7.13(2H, d, J=8.4 Hz),  
7.25(2H, s x2, J=5.7 Hz), 7.41(2H, d, J=8.4 Hz), 8.50(2H, s  
x2, J=5.0 Hz), 8.62(1H, dd, J=5.0, 5.7 Hz), 9.93(1H, s), 11.43  
(1H, s), 12.41(1H, s).

MS: 660(M+Na)<sup>+</sup>

20 Step 2

The title compound was prepared in a similar manner  
according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.17(3H, s), 2.92(2H, m),  
3.23(2H, m), 4.56(2H, m), 7.10-7.31(4H, m), 7.45(4H, br),  
25 8.01(1H, dd, J=8.1, 5.9 Hz), 8.82(1H, d, J=8.0 Hz), 8.84(2H,  
s), 8.96(1H, s), 12.45(1H, s).

MS: 438(M+H)<sup>+</sup> free

**Production Example 83:** Synthesis of 2-(acetylamino)-4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-N-{2-[(2-  
30 phenylacetyl)amino]ethyl}-1,3-thiazole-5-carboxamide  
hydrochloride

Step 1

Di-tert-butyl ((Z)-{4-[2-(2-(acetylamino)-5-[(2-[(2-

phenylacetyl) amino] ethyl) amino) carbonyl] -1,3-thiazol-4-yl] ethyl) phenyl] amino) methylidene) biscardamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 5 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s), 2.15(3H, s), 2.88(2H, m), 3.25-3.31(6H, m), 3.38(2H, s), 7.15-7.44(7H, m), 7.32(2H, d, J=8.3 Hz), 7.98(1H, br), 8.11(1H, br), 9.93(1H, s), 11.43(1H, s), 12.35(1H, s).

10 MS: 730 (M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.90(2H, br), 15 3.20(6H, m), 7.11-7.31(9H, m), 7.38(3H, s), 8.06-8.16(2H, m), 9.75(1H, s), 12.33(1H, s).

MS: 508 (M+H)<sup>+</sup> free

**Production Example 84:** Synthesis of 2-(acetylamino)-4-[2-(4-  
{[amino(imino)methyl] amino} phenyl) ethyl] -N-[5-(dimethylamino)-  
20 5-oxopentyl]-1,3-thiazole-5-carboxamide hydrochloride

#### Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[5-(  
(dimethylamino)-5-oxopentyl] amino) carbonyl)-1,3-thiazol-4-  
yl] ethyl} phenyl) amino] methylidene) biscardamate was prepared  
25 from the compound obtained in Step 2 of Production Example 34  
in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.39-1.50(4H, m), 1.57(9H, s), 2.14(3H, s), 2.29(2H, br), 2.79(3H, s), 2.84-  
30 2.94(2H, m), 2.94(3H, s), 3.15-3.23(4H, m), 7.16(2H, d, J=8.3 Hz), 7.42(2H, d, J=8.3 Hz), 7.97(1H, br), 9.93(1H, s), 11.44(1H, s), 12.35(1H, s).

MS: 696 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39-1.56(4H, m), 2.16(2H, m), 2.29(3H, s), 2.83-2.98(5H, m), 3.06-3.28(4H, m), 7.13(2H, d, J=8.5 Hz), 7.25(2H, d, J=8.5 Hz), 7.40(3H, br), 8.06(1H, br), 9.79(1H, s).

MS: 474 (M+H)<sup>+</sup> free

Production Example 85: Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(benzylamino)-3-oxopropyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(benzylamino)-3-oxopropyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.50(9H, s), 2.15(3H, s), 2.45(2H, t, J=7.2 Hz), 2.73(2H, m), 3.20(2H, m), 3.39(2H, m), 4.26(2H, d, J=5.8 Hz), 7.15-7.28(7H, m), 7.41(2H, d, J=8.4 Hz), 8.02(1H, t, J=5.5 Hz), 8.40(1H, t, J=5.5 Hz), 9.93(1H, s), 11.4(1H, br), 12.3(1H, br).

MS: 730 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.41(2H, t, J=7.0 Hz), 2.90(2H, m), 3.20(2H, m), 3.39(2H, m), 3.63(2H, m), 4.27(2H, d, J=5.8 Hz), 7.11-7.37(9H, m), 7.37(4H, s), 8.09(1H, t, J=5.5 Hz), 8.43(1H, t, J=6.0 Hz), 9.74(1H, s), 12.35(1H, s).

MS: 508 (M+H)<sup>+</sup> free

**Production Example 86:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[6-(dimethylamino)-6-oxohexyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

5 Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[6-(dimethylamino)-6-oxohexyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example  
10 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.13-1.50 (24H, m), 2.14 (3H, s), 2.24 (2H, t, J=8.0 Hz), 2.78 (3H, s), 2.88 (2H, m), 2.92 (3H, s), 3.07-3.25 (4H, m), 7.16 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.95 (1H, t, J=5.52 Hz), 9.94 (1H, s), 11.4 (1H, s),  
15 12.3 (1H, s).

MS: 710 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

20 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.27-1.34 (2H, m), 1.47 (4H, m), 2.16 (3H, s), 2.26 (2H, t, J=7.2 Hz), 2.79 (3H, s), 2.94 (3H, s), 2.90-2.94 (2H, m), 3.17 (4H, m), 7.13 (2H, d, J=8.3 Hz), 7.26 (2H, d, J=8.3 Hz), 7.47 (4H, br), 8.05 (1H, t, J=5.4 Hz), 9.93 (1H, s).

25 MS: 488 (M+H)<sup>+</sup> free

**Production Example 87:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(4-morpholinyl)propyl]-1,3-thiazole-5-carboxamide dihydrochloride

Step 1

30 Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(4-morpholinyl)propyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34

in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.58(9H, br), 1.62(2H, m), 2.14(3H, s), 2.31(6H, m), 2.88(2H, m), 2.19(4H, m), 3.58(4H, m), 7.14(2H, d, J=8.4 Hz), 7.41(2H, d, J=8.4 Hz), 7.95(1H, t, J=5.2 Hz), 9.94(1H, s), 11.45(1H, s), 12.30(1H, s).

MS: 696(M+Na)<sup>+</sup>

### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.90-2.00(2H, br), 2.17(3H, s), 2.83-3.15(6H, m), 3.15-3.30(4H, m), 3.30-3.44(2H, m), 3.77-4.00(4H, m), 7.14(2H, d, J=8.5 Hz), 7.26(2H, d, J=8.5 Hz), 7.44(4H, br), 8.20(1H, t, J=5.5 Hz), 9.92(1H, s), 11.01(1H, s), 12.38(1H, s).

MS: 474(M+H)<sup>+</sup> free

**Production Example 88:** Synthesis of 2-(acetylamino)-4-[2-(4-[[amino(imino)methyl]amino}phenyl)ethyl]-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,3-thiazole-5-carboxamide hydrochloride

### Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[3-(2-oxo-1-pyrrolidinyl)propyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.41(9H, br), 1.49(9H, br), 1.64(2H, t, J=6.9 Hz), 1.90(2H, m), 2.14(3H, s), 2.17(2H, m), 2.91(2H, m), 3.16(6H, m), 3.32(2H, m), 7.16(2H, d, J=8.4 Hz), 7.41(2H, d, J=8.4 Hz), 7.93(1H, t, J=5.6 Hz), 9.93(1H, br), 11.73(1H, br).

MS: 694(M+Na)<sup>+</sup>

### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.65(2H, m), 1.91(2H, m), 2.16(3H, s), 2.20(2H, q, J=7.5 Hz), 2.90(2H, m), 3.02-3.27(6H, m), 3.33(2H, t, J=7.5 Hz), 7.16(2H, d, J=8.5 Hz), 7.26(2H, d, J=8.5 Hz), 8.03(1H, br), 9.92(1H, s), 12.35(1H, s).

MS: 472(M+H)<sup>+</sup> free

**Production Example 89:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-hexyl-1,3-thiazole-5-carboxamide hydrochloride

#### Step 1

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(hexylamino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylenidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 0.85(3H, t, J=6.4 Hz), 1.25(9H, s), 1.35-1.60(17H, br), 2.14(3H, s), 2.88(2H, m), 3.15(4H, m), 7.14(2H, d, J=8.5 Hz), 7.41(2H, d, J=8.5 Hz), 7.92(1H, t, J=5.7 Hz), 10.00(1H, br), 11.60(1H, br).

MS: 653(M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub> (+D<sub>2</sub>O)), δ (ppm): 0.86(3H, t, J=6.53 Hz), 1.18-1.57(8H, m), 2.16(3H, s), 2.91(2H, dd, J=9.5, 6.0 Hz), 3.16(4H, m), 7.13(2H, d, J=8.5 Hz), 7.25(2H, d, J=8.5 Hz), 8.05(1H, br), 9.91(1H, s), 12.33(1H, s).

MS: 431(M+H)<sup>+</sup> free

**Production Example 90:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-oxo-4-(1-piperidinyl)butyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-oxo-4-(1-piperidinyl)butyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
5 from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.29-1.59(20H, m), 1.69(2H, m), 2.14(3H, s), 2.30(2H, t, J=7.5 Hz), 2.89(4H, m), 3.32-  
10 3.45(4H, m), 7.16(2H, d, J=8.0 Hz), 7.41(2H, d, J=8.0 Hz), 7.99(1H, t, J=5.2 Hz), 9.94(1H, s), 11.43(1H, br).

MS: 722 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner  
15 according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.30-1.79(8H, m), 2.16(3H, s), 2.31(2H, t, J=7.5 Hz), 2.92(2H, m), 3.18(4H, m), 3.38(4H, m), 7.13(2H, d, J=8.0 Hz), 7.25(2H, d, J=8.0 Hz), 7.43(4H, br), 8.09(1H, t, J=6.0 Hz), 9.87(1H, s), 12.34(1H, s).

20 MS: 500 (M+H)<sup>+</sup> free

**Production Example 91:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-(4-morpholinyl)-4-oxobutyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

25 Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-(4-morpholinyl)-4-oxobutyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example  
30 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.40(9H, s), 1.50(9H, s), 1.71(2H, m), 2.14(3H, s), 2.32(2H, t, J=7.3 Hz), 2.89(2H, dd, J=10.1, 6.9 Hz), 3.19(4H, m), 3.42(4H, m), 3.51(4H, m),

7.16(2H, d, J=8.3 Hz), 7.42(2H, d, J=8.3 Hz), 7.99(2H, t, J=5.3 Hz), 9.94(1H, s), 11.44(1H, s), 12.33(1H, s).

MS: 724 (M+Na)<sup>+</sup>

### Step 2

5 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.70(2H, m), 2.16(3H, s), 2.33(2H, t, J=7.0 Hz), 2.91(2H, m), 3.19(4H, m), 3.42(4H, m), 3.53(4H, m), 7.13(2H, d, J=8.5 Hz), 7.25(2H, d, J=8.5 Hz),  
10 7.44(4H, br), 8.07(1H, t, J=5.0 Hz), 9.89(1H, s), 12.34(1H, s).

MS: 502 (M+H)<sup>+</sup> free

**Production Example 92:** Synthesis of 2-(acetylamino)-4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-N-[4-  
15 (methylsulfonyl)phenyl]-1,3-thiazole-5-carboxamide  
hydrochloride

### Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-  
(methylthio)phenyl]amino}carbonyl)-1,3-thiazol-4-  
20 yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
from the compound obtained in Step 2 of Production Example 34  
in a similar manner according to Step 1 of Production Example  
32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s),  
25 2.18(3H, s), 2.45(3H, s), 2.82-3.00(2H, m), 3.17-3.30(2H, m),  
7.13(2H, d, J=8.5 Hz), 7.23(2H, d, J=8.5 Hz), 7.41(2H, d,  
J=8.5 Hz), 7.61(2H, d, J=8.5 Hz), 9.92(2H, s), 11.43(1H, s),  
12.45(1H, s).

MS: 691 (M+Na)<sup>+</sup>

### 30 Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[4-  
(methylsulfonyl)phenyl]amino}carbonyl)-1,3-thiazol-4-  
yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in

a similar manner according to Step 2 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 1.51(9H, s),  
2.18(3H, s), 2.81-3.03(2H, m), 3.18(3H, s), 3.19-3.30(2H, m),  
7.16(2H, d, J=8.5 Hz), 7.41(2H, d, J=8.5 Hz), 7.86(2H, d,  
5 J=9.0 Hz), 7.93(2H, d, J=9.0 Hz), 9.92(1H, s), 10.34(1H, s),  
11.42(1H, s), 12.52(1H, s).

MS: 723(M+Na)<sup>+</sup>

### Step 3

The title compound was prepared in a similar manner  
10 according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.20(3H, s), 2.84-3.07(2H,  
m), 3.17-3.32(2H, m), 3.18(3H, s), 7.12(2H, d, J=8.5 Hz),  
7.37(4H, br), 7.86(2H, d, J=9.0 Hz), 7.92(2H, d, J=9.0 Hz),  
9.76(1H, s), 10.42(1H, s).

15 MS: 501(M+H)<sup>+</sup> free

**Production Example 93:** Synthesis of 2-(acetylamino)-4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S)-2-  
(dimethylamino)-1-methyl-2-oxoethyl]-1,3-thiazole-5-  
carboxamide hydrochloride

### 20 Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[(1S)-2-  
(dimethylamino)-1-methyl-2-oxoethyl]amino}carbonyl)-1,3-  
thiazol-4-yl]ethyl}phenyl)amino]methylidene)biscarbamate was  
prepared from the compound obtained in Step 2 of Production

25 Example 34 in a similar manner according to Step 1 of  
Production Example 32.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.40(3H, d, J=7.0 Hz),  
1.49(9H, s), 1.53(9H, s), 2.22(3H, s), 2.95(2H, m), 3.00(3H,  
s), 3.10(3H, s), 3.26(2H, m), 5.01(1H, dt, J=7.0 Hz), 6.87(1H,  
30 d, J=7.5 Hz), 7.14(2H, d, J=8.5 Hz), 7.40(2H, d, J=8.5 Hz),  
9.57(1H, br), 10.20(1H, s), 11.62(1H, s).

MS: 646(M+H)<sup>+</sup>

### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.23(3H, d), 2.16(3H, s), 2.84(3H, s), 2.87-2.95(2H, m), 3.03(3H, s), 3.15-3.24(2H, m),  
5 3.56(1H, s), 4.78(3H, t, J=7.0 Hz), 7.13(2H, d, J=8.4 Hz), 7.25(2H, d, J=8.4 Hz), 8.09(1H, d, J=7.0 Hz), 9.67(1H, s), 12.35(1H, s).

MS: 446(M+H)<sup>+</sup> free

**Production Example 94:** Synthesis of 2-(acetylamino)-4-[2-(4-  
10 {[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S)-1-benzyl-2-(dimethylamino)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

#### Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[(1S)-1-  
15 benzyl-2-(dimethylamino)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

20 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.48(9H, s), 1.52(9H, s), 2.22(3H, s), 2.68(3H, s), 2.84-2.97(5H, m), 3.06(2H, d, J=7.5 Hz), 3.17(H, dd, J=8.0, 6.0 Hz), 5.26(1H, q, J=7.5 Hz), 6.80(1H, d, J=8.0 Hz), 7.08(2H, d, J=8.0 Hz), 7.14-7.33(5H, m), 7.39(2H, d, J=8.0 Hz), 9.96(1H, br), 10.19(1H, s),  
25 11.61(1H, s).

MS: 722(M+H)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

30 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.82-3.15(13H, m), 4.91(1H, q, J=6.7 Hz), 7.09(4H, s), 7.16-7.31(5H, m), 7.36(4H, br), 8.31(1H, d, J=7.7 Hz), 9.71(1H, s), 12.33(1H, s).

MS: 522 (M+H)<sup>+</sup> free

**Production Example 95:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S)-2-(dimethylamino)-1-(hydroxymethyl)-2-oxoethyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({[(1S)-2-(dimethylamino)-1-(hydroxymethyl)-2-oxoethyl]amino}carbonyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene)biscarbamate  
was prepared from the compound obtained in Step 2 of  
Production Example 34 in a similar manner according to Step 1  
of Production Example 32.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.48(9H, s), 1.52(9H, s),  
2.23(3H, s), 2.94(2H, dd, J=7.0 Hz), 3.01(3H, s), 3.14(3H, s),  
3.26(2H, dd, J=7.0 Hz), 3.78-3.86(3H, br), 5.04(1H, m),  
6.85(1H, d, J=7.5 Hz), 7.08(2H, d, J=8.5 Hz), 7.37(2H, d,  
J=8.5 Hz), 9.70(1H, br), 10.20(1H, s), 11.61(1H, s).

MS: 662 (M+H)<sup>+</sup>

Step 2

The title compound was prepared in a similar manner  
according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16, 2.19(3H, s x2), 2.85-  
3.50(10H, m), 3.60-3.69(2H, m), 4.81(1H, m), 7.14(2H, m),  
2.27(2H, m), 7.39(4H, br), 7.91(1H, br), 8.48(1H, br), 9.77,  
9.94(1H, s x2), 12.37, 12.61(1H, s x2).

MS: 462 (M+H)<sup>+</sup> free

**Production Example 96:** Synthesis of 2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-N-[(1S,2S)-1-[(dimethylamino)carbonyl]-2-hydroxypropyl]-1,3-thiazole-5-carboxamide hydrochloride

Step 1

Di-tert-butyl ((Z)-[[4-(2-{2-(acetylamino)-5-[(1S,2S)-1-[(dimethylamino)carbonyl]-2-hydroxypropyl]amino}carbonyl]-

1,3-thiazol-4-yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1 of Production Example 32.

5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.18(3H, d, J=6.5 Hz), 1.48(9H, s), 1.52(9H, s), 2.22(3H, s), 2.95(2H, m), 2.99(3H, s), 3.16(3H, s), 3.20-3.32(2H, m), 4.06-4.12(2H, m), 5.02(1H, dd, J=9.0, 1.5 Hz), 6.55(1H, d, J=9.0 Hz), 7.09(2H, d, J=8.0 Hz), 7.38(2H, d, J=8.0 Hz), 9.70(1H, br), 10.20(1H, s),  
10 11.62(1H, s).

MS: 676(M+H)<sup>+</sup>

#### Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

15 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.35(3H, d, J=6.5 Hz), 2.19(3H, s), 2.85-2.97(6H, m), 3.11(3H, s), 3.26(2H, m), 4.67(1H, br), 5.40(1H, m), 7.15(2H, d, J=8.3 Hz), 7.28(2H, d, J=8.3 Hz), 7.43(4H, br), 8.43(3H, br), 9.93(1H, s), 12.59(1H, s).

20 MS: 475(M+H)<sup>+</sup> free

Production Example 97: Synthesis of (2S)-2-[(2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)carbonyl)amino]-N<sup>1</sup>,N<sup>1</sup>-dimethylpentanediamide hydrochloride  
Step 1

25 Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(1S)-4-amino-1-[(dimethylamino)carbonyl]-4-oxobutyl]amino)carbonyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared from the compound obtained in Step 2 of Production Example 34 in a similar manner according to Step 1  
30 of Production Example 32.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 1.86-2.19(2H, m), 2.22-2.37(5H, m), 2.89(2H, m), 2.99(3H, s), 3.05-3.16(5H, m), 3.20-3.41(1H, m), 5.06(1H, m), 6.27(1H, br),

6.35 (1H, br), 6.81 (1H, d, J=7.5 Hz), 7.09 (2H, d, J=8.5 Hz), 7.41 (2H, d, J=8.5 Hz), 10.21 (1H, s), 10.55 (1H, br), 11.62 (1H, s).

MS: 703 (M+H)<sup>+</sup>

<sup>5</sup> Step 2

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.70-2.00 (2H, m), 2.16 (5H, m), 2.84 (3H, s), 2.91 (2H, m), 3.08 (3H, s), 3.19 (2H, m),  
<sup>10</sup> 4.75 (1H, m), 6.79 (1H, m), 7.12 (2H, d, J=8.3 Hz), 7.25 (2H, d, J=8.3 Hz), 7.39 (4H, br), 8.13 (1H, d), 9.77 (1H, s), 12.35 (1H, s).

MS: 503 (M+H)<sup>+</sup> free

Production Example 98: Synthesis of N-{4-[2-(4-  
<sup>15</sup> {[imino(methylamino)methyl]amino}phenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

The title compound was prepared from the compound obtained in Step 2 of Production Example 50 in a similar manner according to Production Example 58.

<sup>20</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09 (3H, s), 2.79 (3H, s), 2.86 (4H, s), 3.18 (3H, s), 4.08 (2H, s), 4.43 (2H, m), 7.08 (2H, d, J=8.5Hz), 7.22 (2H, d, J=8.5Hz), 7.39 (2H, d, J=8.5Hz), 7.85 (2H, d, J=8.5Hz), 12.05 (1H, brs).

MS: 486 (M+H)<sup>+</sup>

<sup>25</sup> Production Example 99: Synthesis of (2S)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-N,N-dimethyl-2-pyrrolidinecarboxamide dihydrochloride

Step 1

<sup>30</sup> tert-Butyl {4-[2-(2-(acetylamino)-5-{[methoxy(methyl)amino]carbonyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-

5-carboxylic acid in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.46(9H, s), 2.15(3H, s), 2.74-2.93(2H, m), 3.12-3.29(2H, m), 3.22(3H, s), 3.59(3H, s),  
5 7.05(2H, d, J=8.5Hz), 7.33(2H, d, J=8.5Hz), 9.21(1H, s), 12.34(1H, s).

MS: 471.1(M+Na)<sup>+</sup>

### Step 2

To a solution of the compound obtained in Step 1 (3.93 g)  
10 in THF (80 mL) was added lithium aluminium hydride (499 mg) slowly (over 15 min) at 5-10°C (under ice-cooling). The mixture was stirred at 5°C for 1 h. 30 mL of aqueous solution of potassium sodium tartrate (1M) was added slowly under ice-cooling, and then the mixture was stirred for another 0.5 h at  
15 r.t. The mixture was extracted with ethyl acetate, and the organic layer was dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give pale yellow oil. This oil was triturated with IPE and EtOAc to give tert-butyl (4-{2-[2-(acetylamino)-5-formyl-1,3-thiazol-4-yl]ethyl}phenyl)carbamate as pale yellow powder  
20 (2.67g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.46(9H, s), 2.19(3H, s), 2.90(2H, t, J=7.3 Hz), 3.22(2H, t, J=7.3 Hz), 7.01(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 9.22(1H, s), 9.77(1H, s), 12.68(1H, s).

25 MS: 390(M+H)<sup>+</sup>

### Step 3

To a solution of the compound obtained in Step 2 (200 mg) in dichloromethane (6 mL) were added (2S)-2-(N,N-dimethylaminocarbonyl)pyrrolidine hydrochloride and  
30 diisopropylethylamine (0.27 ml) at 5°C. The mixture was stirred at 5°C for 10 min. Then sodium triacetoxyborohydride (327 mg) was added, and the mixture was stirred for 3 hrs. aq. NH<sub>4</sub>Cl was added, and the mixture was extracted with

dichloromethane. The organic layer was dried over  $\text{MgSO}_4$ . The layer was concentrated under reduced pressure. The resulting crude mixture was purified by silica gel column chromatography with mixed solvent (dichloromethane/methanol=15/1) as an  
5 eluent to give tert-butyl (4-{2-[2-(acetylamino)-5-({(2S)-2-[(N,N-dimethylamino)carbonyl]-1-pyrrolidinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl)carbamate as a pale yellow amorphous substance.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 1.67-1.99 (4H, m), 2.24 (3H, s),  
10 2.04 (4H, s), 2.14 (3H, s), 2.95-3.14 (5H, m), 3.42-3.58 (2H, m), 3.68-3.83 (1H, m), 6.97 (2H, d,  $J=8.3$  Hz), 7.94 (2H, d,  $J=8.3$  Hz).

MS: 516 (M+H) $^+$

#### Step 4

15 (2S)-1-({2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl)methyl)-N,N-dimethyl-2-pyrrolidinecarboxamide was prepared in a similar manner according to Step 2 of Production Example 31.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 1.70-2.10 (4H, m), 2.22 (3H, s),  
20 2.39 (1H, q,  $J=8.4$  Hz), 2.77 (4H, m), 2.91 (3H, s), 3.03 (3H, s), 3.30-3.81 (6H, m), 6.58 (2H, d,  $J=8.3$  Hz), 6.89 (2H, d,  $J=8.3$  Hz), 8.82 (1H, br).

MS; 416 (M+H) $^+$

#### Step 5

25 Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(2S)-2-[(N,N-dimethylamino)carbonyl]-1-pyrrolidinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

30  $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 1.50 (9H, s), 1.52 (9H, s), 1.76-1.92 (4H, m), 2.04-2.14 (1H, m), 2.43 (1H, dd,  $J=8.1, 8.0$  Hz), 2.45 (3H, s), 2.85 (2H, s), 3.07 (3H, s), 3.51 (1H, dd,  $J=5.7, 8.0$  Hz), 3.60 (1H, d,  $J=14.3$  Hz), 3.84 (1H, d,  $J=14.3$

Hz), 6.37(1H, t, J=2.0 Hz), 7.08(2H, d, J=8.4 Hz), 7.44(2H, d, J=8.4 Hz), 7.63(1H, d, J=2.0 Hz), 10.23(1H, s), 11.62(1H, br).  
MS: 658 (M+H)<sup>+</sup>

#### Step 6

5 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 1.60-1.98(2H, br), 1.98-2.16(1H, br), 2.16(3H, s), 2.85(3H, s), 2.95(7H, br); 3.00-3.30(1H, br), 7.15(2H, d, J=8.3 Hz), 7.30(2H, d, J=8.3 Hz),  
10 7.55(4H, br), 7.85(1H, d, J=2.2 Hz), 9.65(1H, br), 10.21(1H, s), 12.35(1H, s).

MS: 458 (M+H)<sup>+</sup> free

**Production Example 100:** Synthesis of 3-[(2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl] (methyl) amino]-N,N-dimethylpropanamide  
15 dihydrochloride

#### Step 1

tert-Butyl (4-{2-[2-(acetylamino)-5-({[3-(N,N-dimethylamino)-3-oxopropyl]amino)methyl]-1,3-thiazol-4-yl}ethyl}phenyl)carbamate was prepared from the compound  
20 obtained in Step 2 of Production Example 99 in a similar manner according to Step 3 of Production Example 99.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.50(9H, s), 2.24(3H, s), 2.47(2H, t, J=6.2 Hz), 2.74(2H, t, J=6.2 Hz), 2.82-2.88(4H, m), 2.93(3H, s), 2.97(3H, s), 3.59(2H, s), 6.94(2H, d, J=8.3 Hz), 7.21(2H, d, J=8.3 Hz), 8.02(1H, s).  
25

MS: 490 (M+H)<sup>+</sup>

#### Step 2

To a solution of the compound obtained in Step 1 (100 mg) in dichloromethane (1.5 mL) was added formaline (35%, 87.6 μl).  
30 To this suspension was added 0.05 ml of MeOH. Then, sodium triacetoxyborohydride (433 mg) was added, and the mixture was stirred for 12 hrs. To the mixture were added water and 1N

NaOH to adjust pH of aqueous phase (ca. pH 8-9). The mixture was extracted with dichloromethane. The organic layer was dried with MgSO<sub>4</sub> and concentrated under reduced pressure. Resulting oil was purified by silica gel column chromatography (mixed solvent of CH<sub>2</sub>Cl<sub>2</sub>/MeOH 15/1 as an eluent) to give tert-butyl {4-[2-(2-(acetylamino)-5-[[[3-(N,N-dimethylamino)-3-oxopropyl](methyl)amino]methyl})-1,3-thiazol-4-yl)ethyl]phenyl}carbamate as pale yellow oil (90.4 mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.51(9H, s), 2.18(3H, s), 2.24(3H, s), 2.45(2H, m), 2.62(2H, m), 2.80(4H, s), 2.93(3H, s), 2.99(3H, s), 3.35(2H, s), 6.96(2H, d, J=8.3 Hz), 7.20(2H, d, J=8.3 Hz).

MS: 504 (M+H)<sup>+</sup>

### Step 3

3-[(2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl)methyl(methyl)amino]-N,N-dimethylpropanamide was prepared in a similar manner according to Step 2 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 2.19(3H, s), 2.22(2H, s), 2.43-2.51(2H, m), 2.62-2.71(4H, m), 2.78(3H, s), 2.93(3H, s), 2.99(3H, s), 3.33(2H, s), 3.65(1H, m), 3.75(1H, m), 6.58(2H, d, J=8.3 Hz), 6.87(2H, d, J=8.3 Hz).

MS: 404 (M+H)<sup>+</sup>

### Step 4

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-[[[3-(N,N-dimethylamino)-3-oxopropyl](methyl)amino]methyl})-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared in a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>), δ (ppm): 1.50(9H, s), 1.53(9H, s), 2.20(3H, s), 2.22(3H, s), 2.49(2H, dd, J=6.5, 5.5 Hz), 2.71(2H, dd, J=6.5, 5.5 Hz), 2.84(4H, s), 2.93(3H, s), 2.99(3H, s), 3.43(2H, s), 7.08(2H, d, J=8.4 Hz), 7.46(2H, d,

J=8.4 Hz), 7.62(1H, s), 10.24(1H, s), 11.62(1H, s).

MS: 646(M+H)<sup>+</sup>

#### Step 5

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.68(3H, d, J=4.0 Hz), 2.83-2.88(6H, m), 2.96(6H, s), 3.05-3.15(2H, m), 4.44(2H, m), 7.15(2H, d, J=8.3 Hz), 7.32(2H, d, J=8.3 Hz), 7.62(4H, br), 9.90(1H, s), 12.32(1H, s).

MS: 446(M+H)<sup>+</sup> free

**Production Example 101:** Synthesis of 4-(2-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}ethyl)-N,N-dimethylbenzamide hydrochloride

#### Step 1

Methyl 4-{2-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]vinyl}benzoate was prepared from the compound obtained in Step 2 of Production Example 99 in a similar manner according to Step 1 of Production Example 53.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50(9Hx4/9, s), 1.51(9Hx5/9, s), 2.20(3Hx5/9, s), 2.29(3Hx4/9, s), 2.72-3.06(4H, m), 3.90(3Hx5/9, s), 3.92(3Hx4/9, s), 6.42-6.60(2Hx5/9, m), 6.69(1Hx4/9, d, J=16.6Hz), 6.81-7.03(4H + 1Hx4/9, m), 7.31(2Hx5/9, d, J=8.0Hz), 7.39(2Hx4/9, d, J=8.0Hz), 7.96(2Hx5/9, d, J=8.0Hz), 7.99(2Hx4/9, d, J=8.0Hz).

MS: 522.2(M+H)<sup>+</sup>, 544.2(M+Na)<sup>+</sup>

#### Step 2

Methyl 4-{2-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]ethyl}benzoate was prepared in a similar manner according to Step 6 of Production Example 45.

MS: 524.25(M+H)<sup>+</sup>

#### Step 3

4-{2-[2-(Acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]ethyl}benzoic acid was prepared in a similar manner according to Step 2 of Production Example 65.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.45(9H, s), 2.09(3H, s), 2.57-2.72(6H, m), 2.75-2.86(2H, m), 6.94(2H, d, J=8.4Hz), 7.21(2H, d, J=8.4Hz), 7.32(2H, d, J=8.4Hz), 7.82(2H, d, J=8.4Hz), 9.21(1H, s), 11.94(1H, s), 12.41-13.20(1H, brs).

MS: 510.2(M+H)<sup>+</sup>, 532.2(M+Na)<sup>+</sup>

#### 10 Step 4

tert-Butyl (4-{2-[2-(acetylamino)-5-(2-{4-[(methylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared in a similar manner according to Step 3 of Production Example 65.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.51(9H, s), 2.24(3H, s), 2.56-2.73(4H, m), 2.73-2.86(4H, m), 2.99(3H, d, J=4.8Hz), 6.05(1H, d, J=4.4Hz), 6.25-6.75(1H, brs), 6.77(2H, d, J=6.6Hz), 7.12(2H, d, J=8.1Hz), 7.15-7.23(2H, m), 7.63(2H, d, J=8.1Hz), 8.43-9.18(1H, brs).

20 MS: 523.29(M+H)<sup>+</sup>

#### Step 5

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(2-{4-[(methylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.48(9H, s), 1.54(9H, s), 2.22(3H, s), 2.51-2.61(2H, m), 2.61-2.71(2H, m), 2.79-2.90(4H, m), 2.97(3H, d, J=4.8Hz), 6.20(1H, d, J=4.8Hz), 6.98(2H, d, J=8.4Hz), 7.13(2H, d, J=8.1Hz), 7.40(2H, d, J=8.4Hz), 7.64(2H, d, J=8.4Hz), 8.83-9.42(1H, brs), 10.21(1H, s), 11.62(1H, s).

30 MS: 687.2(M+Na)<sup>+</sup>

#### Step 6

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.58-2.79(6H, m), 2.80-3.02(8H, m), 7.13(2H, d, J=8.4Hz), 7.19(2H, d, J=8.1Hz), 7.20(2H, d, J=8.4Hz), 7.29(2H, d, J=8.1Hz), 7.32(4H, s),  
5 9.66(1H, s), 11.93(1H, s).

MS: 479.2 (M+H)<sup>+</sup> free

**Production Example 102:** Synthesis of 4-(2-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}ethyl)-N-methylbenzamide hydrochloride

10 Step 1

tert-Butyl (4-{2-[2-(Acetylamino)-5-(2-{4-[(dimethylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)carbamate was prepared from the compound obtained in Step 3 of Production Example 101 in a similar  
15 manner according to Step 3 of Production Example 65.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.51(9H, s), 2.23(3H, s), 2.66(4H, s), 2.79(4H, s), 2.93(3H, s), 3.08(3H, s), 6.90(2H, d, J=8.0Hz), 7.11(2H, d, J=8.0Hz), 7.18(2H, d, J=8.0Hz), 8.56-10.01(1H, brs).

20 MS: 537 (M+H)<sup>+</sup>, 559.2 (M+Na)<sup>+</sup>

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(2-{4-[(dimethylamino)carbonyl]phenyl}ethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared in  
25 a similar manner according to Step 4 of Production Example 65.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.21(3H, s), 2.57-2.78(4H, m), 2.82(4H, s), 2.94(3H, s), 3.08(3H, s), 7.03(2H, d, J=8.5Hz), 7.13(2H, d, J=8.0Hz), 7.33(2H, d, J=8.0Hz), 7.45(2H, d, J=8.5Hz), 8.28-9.61(1H, brs), 10.24(1H,  
30 s), 11.63(1H, s).

MS: 679.2 (M+H)<sup>+</sup>, 701.2 (M+Na)<sup>+</sup>

Step 3

The title compound was prepared in a similar manner

according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10(3H, s), 2.60-2.72(4H, m), 2.72-2.80(2H, m), 2.76(3H, d, J=4.4Hz), 2.89(2H, t, J=7.3Hz), 7.12(2H, d, J=8.4Hz), 7.19(2H, d, J=8.4Hz), 7.22(2H, d, J=8.1Hz), 7.33(4H, s), 7.73(2H, d, J=8.1Hz), 8.36(1H, d, J=4.4Hz), 9.66(1H, s), 11.93(1H, s).

MS: 465.2(M+H)<sup>+</sup> free

**Production Example 103:** Synthesis of methyl N-[4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}phenyl)carbamate hydrochloride

#### Step 1

To a suspension of 4-{{2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl)methyl}benzoic acid (50 mg) in toluene (0.5 ml) and dioxane (0.5 ml) were added triethylamine (28.1 μl) and diphenylphosphoryl azide (39.1 μl), and the mixture was stirred at 25°C for 2 hrs., then stirred at 100°C for 1 h. To the reaction mixture was added methanol (1 ml), and the mixture was refluxed for 2 hrs., and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography over silica gel with chloroform / methanol (20:1) as an eluent to give methyl N-(4-{{2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl)methyl}phenyl)carbamate (17.2 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.52(9H, s), 2.22(3H, s), 2.80(4H, s), 3.76(3H, s), 3.79(2H, s), 6.62-6.78(1H, brs), 6.83-7.05(1H, brs), 6.90(2H, d, J=8.0Hz), 6.98(2H, d, J=8.5Hz), 7.17(2H, d, J=8.0Hz), 7.20-7.33(2H, m).

MS: 547.2(M+Na)<sup>+</sup>

#### Step 2

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{4-[(methoxycarbonyl)amino]benzyl)-1,3-thiazol-4-

yl)ethyl]phenyl]amino)methylidene]biscarbamate was prepared in a similar manner according to Step 4 of Production Example 65.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.54(9H, s), 2.19(3H, s), 2.82(4H, s), 3.76(3H, s), 3.80(2H, s), 6.72-6.90(1H, brs),  
5 6.98(2H, d, J=8.5Hz), 7.00(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 7.39(2H, d, J=8.5Hz), 9.10-9.59(1H, brs), 10.19(1H, s), 11.64(1H, s).

MS: 667.2 (M+H)<sup>+</sup>, 689.2 (M+Na)<sup>+</sup>

### Step 3

10 The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08(3H, s), 2.85(4H, s), 3.64(3H, s), 3.85(2H, s), 7.04(2H, d, J=8.5Hz), 7.14(2H, d, J=8.4Hz), 7.24(2H, d, J=8.4Hz), 7.28-7.47(6H, m), 9.58(1H, s), 9.70(1H,  
15 s), 11.96(1H, s).

MS: 467.2 (M+H)<sup>+</sup>

Production Example 104: Synthesis of ethyl 1-({2-(acetylamino)-4-[2-(4-

{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-  
20 yl)methyl)-4-piperidinecarboxylate dihydrochloride

### Step 1

Ethyl 1-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl)methyl)-4-piperidinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-  
25 yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 459.17 (M+H)<sup>+</sup>

### Step 2

Ethyl 1-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-  
30 butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl]-4-piperidinecarboxylate was prepared in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.24(3H, t, J=7.2Hz), 1.50(9H, s), 1.53(9H, s), 1.65-2.09(6H, m), 2.13-2.34(4H, s), 2.71-2.95(6H, m), 3.39(2H, s), 4.12(2H, q, J=7.2Hz), 7.07(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 10.24(1H, s), 11.63(1H, brs).

5 MS: 673.3 (M+H)<sup>+</sup>, 695.3 (M+Na)<sup>+</sup>

### Step 3

The title compound was prepared in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.18(3H, t, J=7.1Hz), 1.73-1.90(2H, 10 m), 1.93-2.13(2H, m), 2.16(3H, s), 2.87-3.01(6H, m), 3.30-3.41(2H, m), 4.08(2H, q, J=7.1Hz), 4.31-4.43(2H, m), 7.15(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz), 7.42(4H, s), 9.90(1H, s), 10.23-10.46(1H, brs), 12.3(1H, s).

MS: 473.2 (M+H)<sup>+</sup>, 495.2 (M+Na)<sup>+</sup> free

15 Production Example 105: Synthesis of ethyl 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}methyl)-4-piperidinecarboxylate hydrochloride

The title compound was prepared in a similar manner 20 according to Example 104.

Production Example 106: Synthesis of 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)-N-[amino(imino)methyl]benzamide

Guanidine hydrochloride (152 mg) was dissolved in DMF (3 25 ml), and then 28 % sodium methoxide methanol solution (0.3 ml) was added to the solution at r.t. The suspension was stirred at r.t. for 15 minutes, and methyl 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)benzoate (150 mg) was added to the mixture at r.t. The reaction mixture was 30 stirred at r.t. for 14 hours, and concentrated *in vacuo*. The residue was dissolved in water, and neutralized with 1N-HCl. The precipitate was collected through filtration, and purified by preparative silica gel chromatography with CHCl<sub>3</sub> / MeOH

(10:1) as an eluent. The solid was washed with ethyl ether to give 4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)-N-[amino(imino)methyl]benzamide (36.6 mg) as an off-white solid.

5 mp. 108-109.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.89(4H, s), 3.16(3H, s), 4.06(2H, s), 7.15(2H, d, J=8.0Hz), 7.27(2H, d, J=8.0Hz), 7.78(2H, d, J=8.0Hz), 7.95(2H, d, J=8.0Hz), 12.04(1H, s).

MS: 500 (M+H)<sup>+</sup>

10 **Production Example 107:** Synthesis of tert-butyl (2-{[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}-2-oxoethyl)carbamate

The title compound was prepared from 2-(acetylamino)-4-[2-(4-aminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol in a similar manner according to Step 1 of Production Example 10.

15 mp. 186-187.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.39(9H, s), 2.08(3H, s), 2.84(4H, s), 3.17(3H, s), 3.71(2H, d, J=6.0Hz), 4.00(2H, s), 7.01(1H, t, J=6.0Hz), 7.06(2H, d, J=8.5Hz), 7.28(2H, d, J=8.5Hz), 7.46(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz), 9.86(1H, s), 12.04(1H, s).

20 MS: 587 (M+H)<sup>+</sup>

**Production Example 108:** Synthesis of N-[4-(2-{2-(acetylamino)-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]-2-aminoacetamide hydrochloride

The title compound was prepared from the compound of Production Example 107 in a similar manner according to Step 2 of Production Example 10.

30 mp. 142.5-144°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.09(3H, s), 2.85(4H, s), 3.18(3H, s), 3.78(2H, m), 4.00(2H, s), 7.10(2H, d, J=8.5Hz), 7.26(2H, d, J=8.5Hz), 7.50(2H, d, J=8.5Hz), 7.79(2H, d, J=8.5Hz),

8.22(3H, brs), 10.63(1H, s), 12.06(1H, s).

MS: 487(M+H)<sup>+</sup> free

**Production Example 109:** Synthesis of N-(4-{2-[4-(2-aminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

5 hydrochloride

Step 1

N-(4-{2-[4-(Cyanomethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide (1 g), 1N-NaOH (7 ml) and EtOH (14 ml) were combined, and the reaction mixture was refluxed for 8 hours.

10 After cooled to r.t., the organic solvent was removed *in vacuo*. The aqueous solution was neutralized with 1N-HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residual yellow wax (1.03 g) was dissolved in THF  
15 (10 ml), and then lithium aluminium hydride (266 mg) was added to the solution at 0°C. The reaction mixture was refluxed for 3 hours, and quenched with MeOH. Then Na<sub>2</sub>SO<sub>4</sub> / 10H<sub>2</sub>O was added to the mixture, the mixture was stirred at r.t. for 1 hour and filtered through a celite pad. The filtrate was concentrated  
20 *in vacuo*. The residual yellow amorphous (835.5 mg) was dissolved in THF (10 ml) and DMF (10 ml) under N<sub>2</sub> atmosphere. Then di(tert-butyl) dicarbonate (841 mg) in THF (5 ml) was added to the solution at r.t. The reaction mixture was stirred at r.t. for 12 hours, and concentrated *in vacuo* to give tert-  
25 butyl (2-{4-[2-(2-amino-1,3-thiazol-4-yl)ethyl]phenyl}ethyl)carbamate (171.6 mg) as yellow oil.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.38(9H, s), 2.60-2.70(4H, m), 2.79-2.88(4H, m), 6.82(1H, s), 7.07(2H, d, J=8.0Hz), 7.11(2H, d, J=8.0Hz).

30 MS: 348(M+H)<sup>+</sup>

Step 2

tert-Butyl [2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl]carbamate was prepared from the compound

of Step 1 in a similar manner according to Step 3 of Production Example 45.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.36(9H, s), 2.11(3H, s), 2.58-2.70(1H, m), 2.80-2.97(6H, m), 3.02-3.18(1H, m), 6.72(1H, s),  
5 7.08(2H, d, J=8.0Hz), 7.23(2H, d, J=8.0Hz), 12.08(1H, s).  
MS: 390 (M+H)<sup>+</sup>

### Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 2 of Production  
10 Example 10.

mp. 165-167°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.12(3H, s), 2.79-3.09(8H, m),  
6.75(1H, s), 7.16(4H, s), 8.14(2H, brs), 12.13(1H, brs).  
MS: 290 (M+H)<sup>+</sup> free

15 Production Example 110: Synthesis of N-(4-{2-[4-(2-[amino(imino)methyl]amino)ethyl]phenyl}ethyl)-1,3-thiazol-2-yl)acetamide hydrochloride

### Step 1

N-(4-{2-[4-(2-Aminoethyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide hydrochloride (7 mg), N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (6.57 mg), N,N-diisopropylethylamine (0.00748 ml), THF (0.5 ml) and DMF (0.1 ml) were combined under N<sub>2</sub> atmosphere. The reaction mixture was stirred at r.t. for 43 hours, and concentrated *in vacuo*.  
25 The residue was purified by preparative silica gel chromatography with *n*-hexane / AcOEt (1:1) as an eluent to give di-tert-butyl ((Z)-{[2-(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)ethyl]amino}-methylidene)biscarbamate (5.9 mg) as colorless oil.

30 <sup>1</sup>H-NMR [CD<sub>3</sub>Cl/CD<sub>3</sub>OD (1:1)], δ (ppm): 1.50(18H, s), 2.24(3H, s), 2.86(2H, t, J=7.0Hz), 2.95(4H, s), 3.62(2H, t, J=7.0Hz), 4.24(2H, s), 6.50(1H, s), 7.11(2H, d, J=8.5Hz), 7.16(2H, d, J=8.5Hz).

MS: 532 (M+H)<sup>+</sup>

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production

5 Example 31.

<sup>1</sup>H-NMR [CD<sub>3</sub>Cl/CD<sub>3</sub>OD (1:1)], δ (ppm): 2.41 (3H, s), 2.87 (2H, t, J=7.0Hz), 3.05 (4H, s), 3.44 (2H, t, J=7.0Hz), 6.86 (1H, s), 7.18 (4H, s).

MS: 332 (M+H)<sup>+</sup> free

10 Production Example 111: Synthesis of N-(4-{4-[(2-{[amino(imino)methyl]amino}ethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl)acetamide hydrochloride

Step 1

1-[4-(Methylthio)phenyl]ethanone (5.5 g) was dissolved in  
15 AcOH (55 ml), and then 90 % pyridinium tribromide (11.8 g) and 30 % hydrobromic acid in AcOH (5.5 ml) were added to the solution at 0°C. The reaction mixture was stirred at r.t. for 30 minutes, and poured into water. The mixture was extracted with AcOEt. The organic layer was washed with saturated NaHCO<sub>3</sub>  
20 and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated in vacuo. The residual solid (8.03 g), thiourea (3.78 g) and EtOH (55 ml) were combined. The reaction mixture was refluxed for 1.5 hours under N<sub>2</sub> atmosphere. After cooled to r.t., the precipitate was filtered in vacuo. The solid was washed with  
25 EtOH and water to give 4-[4-(methylthio)phenyl]-1,3-thiazol-2-amine (7.48 g) as a pale yellow solid.

mp. 245-246°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.51 (3H, s), 7.18 (1H, s), 7.35 (2H, d, J=8.5Hz), 7.67 (2H, d, J=8.5Hz).

30 MS: 223 (M+H)<sup>+</sup>

Step 2

N-{4-[4-(Methylthio)phenyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 1 in a similar manner

according to Step 3 of Production Example 45.

mp. 235-236°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.50(3H, s), 7.31(2H, d, J=8.5Hz), 7.56(1H, s), 7.83(2H, d, J=8.5Hz), 12.24(1H, brs).

MS: 265(M+H)<sup>+</sup>

### Step 3

N-{4-[4-(Methylthio)phenyl]-1,3-thiazol-2-yl}acetamide (2 g) was suspended in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), and then 3-chloroperoxybenzoic acid (1.44 g) was added portionwise to the suspension at 0°C. The reaction mixture was stirred at r.t. for 15 minutes. The precipitate was filtered *in vacuo*, and the solid was washed with 1N-Na<sub>2</sub>CO<sub>3</sub>, water and EtOH to give N-{4-[4-(methylsulfinyl)phenyl]-1,3-thiazol-2-yl}acetamide (2.80 g) as a colorless solid.

mp. 274-274.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10(3H, s), 2.77(3H, s), 7.62(1H, s), 7.71(2H, d, J=8.5Hz), 8.07(2H, d, J=8.5Hz).

MS: 279(M-H)<sup>+</sup>

### Step 4

N-{4-[4-(Methylsulfinyl)phenyl]-1,3-thiazol-2-yl}acetamide (1.5 g), sodium acetate (1.54 g), and acetic anhydride (30 ml) were combined under N<sub>2</sub> atmosphere. The reaction mixture was refluxed for 2 hours. After cooled to r.t., the mixture was diluted in AcOEt. The organic solution was washed with water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residual solid was washed with ethyl ether / n-hexane to give ({4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}thio)methyl acetate (811.2 mg) as an off-white solid.

mp. 144-145°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.07(3H, s), 2.17(3H, s), 5.53(2H, s), 7.50(2H, d, J=8.5Hz), 7.63(1H, s), 7.88(2H, d, J=8.5Hz),

12.27(1H, brs).

MS: 323(M+H)<sup>+</sup>

Step 5

((4-[2-(Acetylamino)-1,3-thiazol-4-yl]phenyl}thio)methyl  
5 acetate (40 mg) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.6 ml) and MeOH (0.3  
ml) under N<sub>2</sub> atmosphere. Then magnesium monoperoxyphthalate  
(120 mg) was added to the solution at 0°C. The reaction  
mixture was stirred at r.t. for 2 hours. Water and CHCl<sub>3</sub> were  
added to the mixture, and the mixture was extracted. The  
10 organic layer was washed with saturated NaHCO<sub>3</sub> and brine, dried  
over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residual  
solid was washed with ethyl ether to give ((4-[2-  
(acetylamino)-1,3-thiazol-4-yl]phenyl)sulfonyl)methyl acetate  
(29.7 mg) as a colorless solid.

15 mp. 237-238°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.07(3H, s), 2.18(3H, s), 5.43(2H,  
s), 7.94(1H, s), 7.97(2H, d, J=8.5Hz), 8.17(2H, d, J=8.5Hz),  
12.37(1H, brs).

MS: 355(M+H)<sup>+</sup>

20 Step 6

((4-[2-(Acetylamino)-1,3-thiazol-4-  
yl]phenyl)sulfonyl)methyl acetate (700 mg), THF (8 ml), MeOH  
(4 ml) and 1N-NaOH (1.98 ml) were combined. The reaction  
mixture was stirred at r.t. for 1.5 hours, and concentrated *in*  
25 *vacuo*. The residual solid was washed with ethyl ether to give  
sodium 4-[2-(acetylamino)-1,3-thiazol-4-yl]phenylsulfinate  
(731 mg) as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 7.52(2H, d, J=8.0Hz),  
7.54(1H, s), 7.84(2H, d, J=8.0Hz).

30 MS: 281(M-H)<sup>+</sup> free

Step 7

Sodium 4-[2-(acetylamino)-1,3-thiazol-4-  
yl]phenylsulfinate (600 mg) was dissolved in DMF (2 ml) under

N<sub>2</sub> atmosphere. Then 2-bromoethanol (0.168 ml) was added to the solution at 0°C. The reaction mixture was stirred at 100°C for 7 hours. After cooled to r.t., water and AcOEt were added to the mixture. The precipitate was filtered *in vacuo* to give N-  
5 (4-{4-[(2-hydroxyethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl)acetamide (80.2 mg) as an off-white solid.

mp. 258-260°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 3.47(2H, t, J=6.0Hz),  
3.70(2H, q, J=6.0Hz), 4.89(1H, t, J=6.0Hz), 7.89(1H, s),  
10 7.94(2H, d, J=8.5Hz), 8.13(2H, d, J=8.5Hz), 12.36(1H, brs).

MS: 325 (M-H)<sup>+</sup>

#### Step 8

N-(4-{4-[(2-Hydroxyethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl)acetamide (200 mg), Et<sub>3</sub>N (0.102 ml) and CH<sub>2</sub>Cl<sub>2</sub> (4 ml) were  
15 combined under N<sub>2</sub> atmosphere, and then MsCl (0.05 ml) was added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 2 hours. MeOH/CHCl<sub>3</sub> and water were added to the mixture, and the mixture was extracted. The organic layer was washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated  
20 *in vacuo*. The residual solid (221.6 mg) was suspended in CH<sub>3</sub>CN (10 ml), and then 28 % ammonia solution (0.5 ml) was added to the suspension at 0°C. The reaction mixture was stirred at r.t. for 15 hours, and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with  
25 [MeOH/CHCl<sub>3</sub> (1:30), then NH<sub>4</sub>OH/MeOH/CHCl<sub>3</sub> (1:10:60)] as an eluent, and triturated with EtOH / ethyl ether to give N-(4-{4-[(2-aminoethyl)sulfonyl]phenyl}-1,3-thiazol-2-yl)acetamide (60.4 mg) as an off-white solid.

mp. 287-288°C

30 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 2.79(2H, t, J=6.5Hz),  
3.36(2H, q, J=6.5Hz), 7.90(1H, s), 7.94(2H, d, J=8.5Hz),  
8.15(2H, d, J=8.5Hz).

MS: 326 (M+H)<sup>+</sup>

Step 9

Di-tert-butyl ((Z)-{[2-({4-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl)sulfonyl}ethyl)amino}methylenidene)biscarbamate was prepared from the compound of Step 8 in a similar manner according to Step 3 of Production Example 31.

mp. 280-281°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.38(9H, s), 1.39(9H, s), 2.18(3H, s), 3.65(4H, s), 7.88(1H, s), 7.93(2H, d, J=8.5Hz), 8.13(2H, d, J=8.5Hz), 8.32(1H, brs), 11.32(1H, brs), 12.35(1H, brs).

MS: 568 (M+H)<sup>+</sup>

Step 10

The title compound was prepared from the compound of Step 9 in a similar manner according to Step 4 of Production Example 31.

mp. 188-189.5°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.18(3H, s), 3.51(2H, m), 3.59(2H, t, J=6.0Hz), 7.28(3H, brs), 7.62(1H, t, J=5.5Hz), 7.93(1H, s), 7.98(2H, d, J=8.5Hz), 8.17(2H, d, J=8.5Hz), 12.37(1H, brs).

MS: 368 (M+H)<sup>+</sup> free

**Production Example 112:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[3-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

N-Methoxy-N-methyl-3-(methylsulfonyl)benzamide was prepared from 3-(methylsulfonyl)benzoic acid in a similar manner according to Step 1 of Production Example 31.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 3.08(3H, s), 3.40(3H, s), 3.55(3H, s), 7.64(1H, t, J=8.0Hz), 7.99(1H, dt, J=8.0, 1.5Hz), 8.03(1H, dt, J=8.0, 1.5Hz), 8.28(1H, t, J=1.5Hz).

MS: 244 (M+H)<sup>+</sup>

Step 2

To a stirred solution of N-methoxy-N-methyl-3-

(methylsulfonyl)benzamide (5 g) in dry THF (100 ml) was added dropwise DIBALH (22.6 ml) at  $-78^{\circ}\text{C}$  under  $\text{N}_2$  atmosphere. The reaction mixture was stirred for 4 hours at r.t. and then quenched with MeOH at  $0^{\circ}\text{C}$ . AcOEt and 1N-HCl were added to the  
5 mixture, and extracted. The organic layer was washed with brine, dried over anhydrous  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residual oil (3.38 g), methyl (triphenylphosphoranylidene)acetate (6.87 g) and THF (68 ml) were combined at r.t. under  $\text{N}_2$  atmosphere, and the reaction  
10 mixture was refluxed for 3 hours. The solvent was removed *in vacuo*, and the residue was suspended in AcOEt. The solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / AcOEt (2:1) as an eluent to give  
15 methyl (2E)-3-[3-(methylsulfonyl)phenyl]acrylate (613.8 mg) as yellow oil.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 3.28(3H, s), 3.75(3H, s), 6.85(1H, d,  $J=16.0\text{Hz}$ ), 7.74(1H, s), 7.93(1H, t,  $J=8.0\text{Hz}$ ), 7.96(1H, d,  $J=8.0\text{Hz}$ ), 8.09(1H, d,  $J=8.0\text{Hz}$ ), 8.32(1H, d,  $J=16.0\text{Hz}$ ).

#### 20 Step 3

Methyl (2E)-3-[3-(methylsulfonyl)phenyl]acrylate (600 mg), MeOH (6 ml) and then 10 % palladium carbon (99.9 mg) were combined under  $\text{N}_2$  atmosphere. The reaction mixture was stirred at r.t. for 7 hours under  $\text{H}_2$  atmosphere (1 atm), and filtered  
25 through a celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with n-hexane / AcOEt (1:1  $\rightarrow$  1:2) as an eluent to give methyl 3-[3-(methylsulfonyl)phenyl]propanoate (283.3 mg) as colorless oil.

30  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ),  $\delta$  (ppm): 2.70(2H, t,  $J=7.5\text{Hz}$ ), 2.97(2H, t,  $J=7.5\text{Hz}$ ), 3.20(3H, s), 3.58(3H, s), 7.52-7.63(2H, m), 7.73-7.80(2H, m).

#### Step 4

Ethyl 4-[3-(methylsulfonyl)phenyl]-2-oxobutanoate was prepared from the compound of Step 3 in a similar manner according to Step 2 of Production Example 47.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.35(3H, t, J=7.0Hz), 3.05(2H, t, J=7.0Hz), 3.06(3H, s), 3.24(2H, t, J=7.0Hz), 4.32(2H, q, J=7.0Hz), 7.45-7.82(4H, m).

#### Step 5

Ethyl 3-bromo-4-[3-(methylsulfonyl)phenyl]-2-oxobutanoate was prepared from the compound of Step 4 in a similar manner according to Step 1 of Production Example 46.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.37(3H, t, J=7.0Hz), 3.07(3H, s), 3.34(1H, dd, J=14.5, 8.0Hz), 3.60(1H, dd, J=14.5, 6.5Hz), 4.35(2H, q, J=7.0Hz), 5.26(1H, dd, J=8.0, 6.5Hz), 7.49-7.88(4H, m).

#### Step 6

Ethyl 2-amino-5-[3-(methylsulfonyl)benzyl]-1,3-thiazole-4-carboxylate was prepared from the compound of Step 5 in a similar manner according to Step 2 of Production Example 46.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.24(3H, t, J=7.0Hz), 3.20(3H, s), 4.20(2H, q, J=7.0Hz), 4.46(2H, s), 7.10(2H, s), 7.57-7.61(2H, m), 7.76-7.83(2H, m).

MS: 341 (M+H)<sup>+</sup>

#### Step 7

Ethyl 2-(acetylamino)-5-[3-(methylsulfonyl)benzyl]-1,3-thiazole-4-carboxylate was prepared from the compound of Step 6 in a similar manner according to Step 3 of Production Example 45.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.27(3H, t, J=7.0Hz), 2.10(3H, s), 3.20(3H, s), 4.27(2H, q, J=7.0Hz), 4.61(2H, s), 7.56-7.66(2H, m), 7.77-7.89(2H, m), 12.47(1H, s).

MS: 383 (M+H)<sup>+</sup>

#### Step 8

Ethyl 2-(acetylamino)-5-[3-(methylsulfonyl)benzyl]-1,3-

thiazole-4-carboxylate (54.7 mg) was suspended in THF (1 ml) under N<sub>2</sub> atmosphere, and then lithium aluminium hydride (7.79 mg) was added portionwise to the suspension at 0°C. The reaction mixture was refluxed for 2.5 hours, and quenched with 5 MeOH and 1N-HCl at 0°C. Anhydrous MgSO<sub>4</sub> was added to the mixture, and stirred at r.t. for 1 hour. The suspension was filtered *in vacuo*. The filtrate was concentrated *in vacuo*. The residual oil (114.8 mg), CHCl<sub>3</sub> (1 ml), CH<sub>3</sub>CN (1 ml) and Dess-Martin periodinane (88 mg) were combined at 0°C under N<sub>2</sub> 10 atmosphere. The reaction mixture was stirred at r.t. for 1 hour, and diluted in CHCl<sub>3</sub>. The organic solution was washed with saturated NaHCO<sub>3</sub>, water and brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo* to give N-{4-formyl-5-[3-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (61.2mg) as 15 a yellow amorphous.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.13(3H, s), 3.17(3H, s), 4.67(2H, s), 7.56-7.90(4H, m), 10.04(1H, s), 12.39(1H, s).

#### Step 9

N-{5-[3-(Methylsulfonyl)benzyl]-4-[(Z)-2-(4- 20 nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 8 in a similar manner according to Step 5 of Production Example 45.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.08(3Hx2/3, s), 2.13(3Hx1/3, s), 3.18(3H, s), 4.23(2Hx2/3, s), 4.50(2Hx1/3, s), 6.69-8.31(10H, 25 m).

#### Step 10

N-{4-[2-(4-Aminophenyl)ethyl]-5-[3-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 9 in a similar manner 30 according to Step 6 of Production Example 45.

MS: 430 (M+H)<sup>+</sup>

#### Step 11

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[3-

(methylsulfonyl)benzyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared from the compound of Step 10 in a similar manner according to Step 3 of Production Example 31.

5 <sup>1</sup>H-NMR [CD<sub>3</sub>Cl/CD<sub>3</sub>OD (1:1)], δ (ppm): 1.29(9H, s), 1.55(9H, s), 2.23(3H, s), 2.89(4H, m), 3.07(3H, s), 3.90(2H, s), 7.11-7.87(8H, m).

MS: 672 (M+H)<sup>+</sup>

#### Step 12

10 The title compound was prepared from the compound of Step 11 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD), δ (ppm): 2.08(3H, s), 2.98(4H, m), 3.10(3H, s), 3.98(2H, s), 7.10-7.88(8H, m).

15 MS: 472 (M+H)<sup>+</sup> free

**Production Example 113:** Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1,3-thiazol-2-yl}acetamide dihydrochloride

#### 20 Step 1

N-{5-[(1,1-Dioxido-4-thiomorpholinyl)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of

25 Production Example 67.

MS: 437.12 (M+H)<sup>+</sup>

#### Step 2

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1,3-thiazol-4-

30 yl}ethyl)phenyl]amino)methylidene)biscarbamate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.23(3H, s),

2.70-2.95 (8H, m), 2.95-3.12 (4H, s), 3.45 (2H, s), 6.99 (2H, d, J=8.3Hz), 7.42 (2H, d, J=8.3Hz), 8.94-9.24 (1H, brs), 10.24 (1H, s), 11.63 (1H, s).

MS: 651.1 (M+H)<sup>+</sup>, 673.3 (M+Na)<sup>+</sup>

<sup>5</sup> Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15 (3H, s), 2.97 (4H, s), 3.77-  
<sup>10</sup> 4.63 (8H, s), 4.45 (2H, s), 7.15 (2H, d, J=8.3Hz), 7.32 (2H, d, J=8.3Hz), 7.46 (4H, s), 9.96 (1H, s), 12.29 (1H, s).

MS: 451.3 (M+H)<sup>+</sup>, 473.2 (M+Na)<sup>+</sup>

Production Example 114: Synthesis of N-[4-[2-(4-  
{[amino(imino)methyl]amino}phenyl)ethyl]-5-(4-  
<sup>15</sup> morpholinylmethyl)-1,3-thiazol-2-yl]acetamide dihydrochloride  
Step 1

N-{5-(4-Morpholinylmethyl)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-  
<sup>20</sup> yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 389.16 (M+H)<sup>+</sup>

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(4-morpholinylmethyl)-1,3-thiazol-4-  
<sup>25</sup> yl]ethyl}phenyl)amino]methylidene)biscarbamate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.53 (9H, s), 2.22 (3H, s),  
<sup>30</sup> 2.30-2.46 (4H, m), 2.85 (4H, s), 3.39 (2H, s), 3.58-3.75 (4H, m), 7.07 (2H, d, J=8.4Hz), 7.45 (2H, d, J=8.4Hz), 8.80-9.31 (1H, brs), 10.24 (1H, s), 11.63 (1H, s).

MS: 603.3 (M+H)<sup>+</sup>

Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16 (3H, s), 2.97 (4H, s), 3.00-3.12 (2H, m), 3.16-3.27 (2H, m), 3.65-3.76 (2H, m), 3.86-3.97 (2H, m), 4.43 (2H, s), 7.15 (2H, d, J=8.4Hz), 7.31 (2H, d, J=8.4Hz), 7.40 (4H, s), 9.86 (1H, s), 10.54-10.84 (1H, brs), 12.34 (1H, s).  
MS: 403.1 (M+H)<sup>+</sup>, 426.1 (M+Na)<sup>+</sup>

Production Example 115: Synthesis of N-{4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-[(3-oxo-1-piperazinyl)methyl]-1,3-thiazol-2-yl}acetamide dihydrochloride  
Step 1

N-{4-[(Z)-2-(4-Nitrophenyl)vinyl]-5-[(3-oxo-1-piperazinyl)methyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

Z : E = 3 : 1

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10 (3Hx3/4, s), 2.15 (3Hx1/4, s), 2.54-2.59 (2Hx3/4, m), 2.61-2.67 (2Hx1/4, m), 2.93 (2Hx3/4, s), 3.02 (2Hx1/4, m), 3.08-3.19 (2H, m), 3.64 (2Hx3/4, s), 3.95 (2Hx1/4, s), 6.72 (1Hx3/4, d, J=12.4Hz), 6.78 (1Hx3/4, d, J=12.4Hz), 7.34 (1Hx1/4, d, J=15.7Hz), 7.59 (1x1/4, d, J=15.7Hz), 7.62 (2Hx3/4, d, J=8.8Hz), 7.76 (1Hx3/4, s), 7.78 (1Hx1/4, s), 7.90 (2Hx1/4, d, J=8.8Hz), 8.14 (2Hx3/4, d, J=8.8Hz), 8.21 (2Hx1/4, d, J=8.8Hz), 11.75-12.06 (1Hx3/4, brs), 12.08-12.33 (1Hx1/4, brs).

MS: 402.21 (M+H)<sup>+</sup>

Step 2

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[(3-oxo-1-piperazinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylenidene)biscarbamate was prepared

from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.24(3H, s), 2.47-2.55(2H, m), 2.80-2.93(4H, m), 3.13(2H, s), 3.24-3.32(2H, m), 3.43(2H, s), 6.02(1H, s), 7.04(2H, d, J=8.4Hz), 7.44(2H, d, J=8.3Hz), 9.02-9.26(1H, brs), 10.24(1H, s), 11.62(1H, s).  
MS: 616.2 (M+H)<sup>+</sup>, 638.2 (M+Na)<sup>+</sup>

### Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.15(3H, s), 2.39-2.62(2H, m), 2.95(4H, s), 3.08-3.86(4H, m), 4.20-4.77(2H, brs), 7.15(2H, d, J=8.3Hz), 7.30(2H, d, J=8.0Hz), 7.35(4H, s), 8.04-8.62(1H, brs), 9.70(1H, s), 10.67-11.38(1H, brs), 11.97-12.72(1H, brs).  
MS: 416.2 (M+H)<sup>+</sup> free

**Production Example 116:** Synthesis of 4-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-N,N-dimethyl-1-piperazinecarboxamide

dihydrochloride

### Step 1

9H-Fluoren-9-ylmethyl 4-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl)methyl}-1-piperazinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.10(3H, s), 2.26-2.61(4H, m), 3.39-3.64(6H, m), 4.19-4.30(1H, m), 4.37-4.49(2H, m), 6.66(2H, s), 7.07-7.67(8H, m), 7.76(2H, d, J=6.9Hz), 8.05(2H, d, J=8.9Hz), 10.03(1H, s).

MS: 610.2 (M+H)<sup>+</sup>, 632.2 (M+Na)<sup>+</sup>

### Step 2

9H-Fluoren-9-ylmethyl 4-({2-(acetylamino)-4-[2-(4-

aminophenyl)ethyl]-1,3-thiazol-5-yl)methyl)-1-

piperazinecarboxylate was prepared from the compound of Step 1 in a similar manner according to Step 6 of Production Example 45.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.16-2.33 (7H, m), 2.80 (4H, s), 3.34 (2H, s), 3.36-3.84 (6H, m), 4.17-4.30 (1H, m), 4.36-4.47 (2H, m), 6.57 (2H, d, J=8.4Hz), 6.86 (2H, d, J=8.3Hz), 7.26-7.46 (4H, m), 7.56 (2H, d, J=7.0Hz), 7.76 (2H, d, J=6.9Hz), 8.60-9.52 (1H, brs).

MS: 582.2 (M+H)<sup>+</sup>, 604.3 (M+Na)<sup>+</sup>

### Step 3

9H-Fluoren-9-ylmethyl 4-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl)amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-1-piperazinecarboxylate was prepared from the compound of Step 2 in a similar manner according to Step 3 of Production Example 31.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.52 (9H, s), 2.23 (3H, s), 2.28-2.43 (4H, m), 2.86 (4H, s), 3.36-3.55 (6H, m), 4.18-4.29 (1H, m), 4.35-4.48 (2H, m), 7.05 (2H, d, J=8.5Hz), 7.13-7.66 (8H, m), 7.75 (2H, d, J=7.0Hz), 8.85-9.76 (1H, brs), 10.25 (1H, ss), 11.63 (1H, s).

MS: 824.2 (M+H)<sup>+</sup>, 847.3 (M+Na)<sup>+</sup>

### Step 4

To a solution of 9H-fluoren-9-ylmethyl 4-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino][(tert-butoxycarbonyl)imino]methyl)amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-1-piperazinecarboxylate (400 mg) in DMF (0.8 ml) was added piperidine (0.16 ml), and the mixture was stirred for 2 h at 20°C. To the reaction mixture was added piperidine (0.16 ml), stirred at 20°C for 1 h and 40°C for 1 h, then cooled to 20°C, added AcOEt (50 ml), and the mixture was

washed with water (10 mlx3) and brine (10 ml), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give crude pale yellow oil (463 mg). The crude oil was purified by flash column chromatography over NH silica gel with dichloromethane / methanol (100:0) → (100 : 1) as an eluent to give di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(1-piperazinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate as a colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.53 (9H, s), 2.21 (3H, s), 2.27-2.47 (4H, m), 2.71-3.00 (8H, m), 3.40 (2H, s), 7.07 (2H, d, J=8.4Hz), 7.45 (2H, d, J=8.4Hz), 10.24 (1H, s), 11.47-11.74 (1H, brs).

MS: 602.3 (M+H)<sup>+</sup>, 624.2 (M+Na)<sup>+</sup>

#### Step 5

To a solution of di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(1-piperazinylmethyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate (30 mg) in dichloromethane (0.3 ml) were added N,N-diisopropylethylamine (9.55 μl) and dimethylcarbamy l chloride (4.59 μl), and the mixture was stirred for 14 h at 20°C. To the reaction mixture was added saturated sodium hydrogen carbonate aqueous solution (2 ml), then the mixture was extracted with dichloromethane (5 mlx3) and the extract was dried over diatomaceous earth. The organic layer was concentrated *in vacuo* to give crude oil. The residue was purified by preparative silica gel thin-layer chromatography with chloroform / methanol (20:1) as an eluent to give di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(dimethylamino)carbonyl]-1-piperazinyl}methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate as colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.54 (9H, s), 2.23 (3H, s), 2.35-2.42 (4H, m), 2.80 (6H, s), 2.81-2.89 (4H, m), 3.17-3.27 (4H, m), 3.41 (2H, s), 7.07 (2H, d, J=8.4Hz), 7.46 (2H, d, J=8.4Hz),

8.73-8.90 (1H, brs), 10.25 (1H, s), 11.63 (1H, s).

MS: 673.3 (M+H)<sup>+</sup>, 695.2 (M+Na)<sup>+</sup>

#### Step 6

The title compound was prepared from the compound of Step 5 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16 (3H, s), 2.76 (6H, s), 2.91-3.06 (6H, m), 3.07-3.19 (2H, m), 3.20-3.30 (2H, m), 3.57-3.65 (2H, m), 4.36-4.51 (2H, m), 7.15 (2H, d, J=8.4Hz), 7.31 (2H, d, J=8.4Hz), 7.41 (4H, s), 9.87 (1H, s), 10.51-10.69 (1H, brs), 12.33 (1H, s).

MS: 473.2 (M+H)<sup>+</sup>

**Production Example 117:** Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(4-morpholinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-2-yl)acetamide dihydrochloride

#### Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetyl amino)-5-{[4-(4-morpholinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 4 of Production Example 116 in a similar manner according to Step 5 of Production Example 116.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.54 (9H, s), 2.23 (3H, s), 2.32-2.46 (4H, m), 2.78-2.91 (4H, m), 3.20-3.30 (8H, m), 3.42 (2H, s), 3.63-3.71 (4H, m), 7.07 (2H, d, J=8.4Hz), 7.46 (2H, d, J=8.4Hz), 8.72-8.89 (1H, brs), 10.25 (1H, s), 11.64 (1H, s).

MS: 715.3 (M+H)<sup>+</sup>, 737.2 (M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16 (3H, s), 2.90-3.07 (6H, m), 3.11-3.32 (8H, m), 3.48-3.76 (6H, m), 4.42 (2H, s), 7.15 (2H, d,

J=8.4Hz), 7.31 (2H, d, J=8.4Hz), 7.40 (4H, s), 9.85 (1H, s), 10.51-10.72 (1H, brs), 12.34 (1H, s).

MS: 515.3 (M+H)<sup>+</sup> free

**Production Example 118:** Synthesis of N-(4-[2-(4-

5 { [amino(imino)methyl]amino}phenyl)ethyl]-5-{[4-(1-pyrrolidinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-2-yl)acetamide dihydrochloride

**Step 1**

Di-tert-butyl [(Z)-({4-[2-(2-(acetyl amino)-5-{[4-(1-  
10 pyrrolidinylcarbonyl)-1-piperazinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 4 of Production Example 116 in a similar manner according to Step 5 of Production Example 116.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.54 (9H, s), 1.72-  
15 1.89 (4H, m), 2.23 (3H, s), 2.28-2.48 (4H, m), 2.84 (4H, s), 3.19-3.39 (8H, m), 3.41 (2H, s), 7.07 (2H, d, J=8.4Hz), 7.46 (2H, d, J=8.4Hz), 8.71-8.99 (1H, brs), 10.24 (1H, s), 11.64 (1H, s).  
MS: 699.2 (M+H)<sup>+</sup>, 721.3 (M+Na)<sup>+</sup>

**Step 2**

20 The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.70-1.83 (4H, m), 2.16 (3H, s), 2.89-3.05 (6H, m), 3.06-3.19 (2H, m), 3.20-3.32 (6H, m), 3.64-3.84 (2H,  
25 m), 4.36-4.50 (2H, m), 7.15 (2H, d, J=8.2Hz), 7.31 (2H, d, J=8.3Hz), 7.42 (4H, s), 9.88 (1H, s), 10.50-10.75 (1H, brs), 12.34 (1H, s).

MS: 499.3 (M+H)<sup>+</sup> free

**Production Example 119:** Synthesis of N-[4-[2-(4-

30 { [amino(imino)methyl]amino}phenyl)ethyl]-5-({4-[(4-methyl-1-piperazinyl)carbonyl]-1-piperazinyl}methyl)-1,3-thiazol-2-yl)acetamide trihydrochloride

**Step 1**

Di-tert-butyl ((Z)-[(4-{2-[2-(acetylamino)-5-({4-[(4-methyl-1-piperazinyl)carbonyl]-1-piperazinyl)methyl]-1,3-thiazol-4-yl}ethyl)phenyl)amino]methylidene)biscarbamate was prepared from the compound of Step 4 of Production Example 116 in a similar manner according to Step 5 of Production Example 116.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50(9H, s), 1.54(9H, s), 2.23(3H, s), 2.29(3H, s), 2.32-2.48(8H, m), 2.84(4H, s), 3.16-3.35(8H, m), 3.42(2H, s), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.69-9.04(1H, brs), 10.24(1H, s), 11.64(1H, s).

MS: 728.2 (M+H)<sup>+</sup>, 750.3 (M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.76(3H, d, J=4.6Hz), 2.89-3.09(8H, m), 3.17-3.39(8H, m), 3.62-3.77(4H, m), 4.34-4.51(2H, brs), 7.15(2H, d, J=8.3Hz), 7.31(2H, d, J=8.2Hz), 7.41(4H, s), 9.87(1H, s), 10.68-10.97(1H, brs), 12.34(1H, s).  
MS: 528.3 (M+H)<sup>+</sup> free

**Production Example 120:** Synthesis of 3-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}-N,N-dimethylpropanamide hydrochloride

#### Step 1

Ethyl 3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]acrylate was prepared from 2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazole-5-carbaldehyde in a similar manner according to Step 7 of Production Example 61.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.16-1.40(3H, m), 1.52(9H, s), 2.23-2.38(3H, m), 2.70-3.06(4H, m), 4.15-4.33(2H, m), 5.53-6.15(1H, m), 6.64-7.85(6H, m).

MS: 482.2 (M+Na)<sup>+</sup>Step 2

A mixture of ethyl (2E)-3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]acrylate and ethyl (2Z)-3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]acrylate (200 mg), THF (7 ml) and 10 % Pd/C (392 mg) were combined under nitrogen atmosphere. The mixture was stirred under 3 atm hydrogen atmosphere at 20°C for 3 h. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated *in vacuo* to give ethyl 3-[2-(acetylamino)-4-(2-{4-[(tert-butoxycarbonyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl]propanoate as a colorless amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.24(3H, t, J=7.0Hz), 1.51(9H, s), 2.24(3H, s), 2.41(2H, t, J=7.5Hz), 2.73-2.93(6H, m), 4.12(2H, q, J=7.0Hz), 6.95(2H, d, J=7.2Hz), 7.23(2H, d, J=7.7Hz).

MS: 484.1 (M+Na)<sup>+</sup>Step 3

Ethyl 3-(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl)propanoate was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 65.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.24(3H, t, J=7.1Hz), 1.50(9H, s), 1.53(9H, s), 2.21(3H, s), 2.41(2H, t, J=7.6Hz), 2.70-3.00(6H, m), 4.12(2H, q, J=7.2Hz), 7.07(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.80-9.20(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 604.3 (M+H)<sup>+</sup>, 626.2 (M+Na)<sup>+</sup>Step 4

3-(2-(Acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl)propanoic acid was prepared from the compound of Step 3 in

a similar manner according to Step 1 of Production Example 42.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.47(9H, s), 1.53(9H, s), 2.19(3H, s), 2.25-2.45(2H, m), 2.60-3.00(6H, m), 6.96(2H, d, J=8.3Hz), 7.34(2H, d, J=8.3Hz), 10.17(1H, s), 11.30-11.90(1H, brs).

5 MS: 598.2(M+Na)<sup>+</sup>

#### Step 5

Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[3-(dimethylamino)-3-oxopropyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared  
10 from the compound of Step 4 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.21(3H, s), 2.28-2.43(2H, m), 2.79-2.99(12H, m), 7.05(2H, d, J=8.5Hz), 7.44(2H, d, J=8.5Hz), 8.85-9.37(1H, brs), 10.23(1H, s),  
15 11.62(1H, s).

MS: 603.3(M+H)<sup>+</sup>, 625.3(M+Na)<sup>+</sup>

#### Step 6

The title compound was prepared from the compound of Step 5 in a similar manner according to Step 4 of Production  
20 Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10(3H, s), 2.40(2H, t, J=7.3Hz), 2.75(2H, t, J=7.3Hz), 2.77-2.84(5H, m), 2.84-2.95(5H, m), 7.14(2H, d, J=8.4Hz), 7.24(2H, d, J=8.4Hz), 7.36(4H, s), 9.72(1H, s), 11.93(1H, s).

25 MS: 403.3(M+H)<sup>+</sup> free

**Production Example 121:** Synthesis of 3-{2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl}-N-methylpropanamide hydrochloride

#### Step 1

30 Di-tert-butyl ((Z)-{[4-(2-{2-(acetylamino)-5-[3-(methylamino)-3-oxopropyl]-1,3-thiazol-4-yl}ethyl)phenyl]amino}methylidene)biscarbamate was prepared from the compound of Step 4 of Production Example 120 in a

similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.45(9H, s), 1.54(9H, s), 1.79-  
1.88(2H, s), 2.23(3H, s), 2.65(3H, d, J=4.8Hz), 2.69-2.77(2H,  
m), 2.79-2.86(2H, m), 2.86-2.95(2H, m), 6.04(2H, d, J=4.4Hz),  
5 6.93(2H, d, J=8.4Hz), 7.28(2H, d, J=8.4Hz), 8.79-9.17(1H,  
brs), 10.28(1H, s), 11.60(1H, s).

MS: 589.3(M+H)<sup>+</sup>, 611.3(M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared from the compound of Step  
10 1 in a similar manner according to Step 4 of Production  
Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10(3H, s), 2.22(2H, t, J=7.3Hz),  
2.53(3H, d, J=4.8Hz), 2.72-2.82(4H, m), 2.82-2.90(2H, m),  
7.15(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 7.38(4H, s),  
15 7.79(1H, d, J=4.5Hz), 9.76(1H, s), 11.95(1H, s).

MS: 389.2(M+H)<sup>+</sup>, 411.2(M+Na)<sup>+</sup> free

**Production Example 122:** Synthesis of 3-{2-(acetylamino)-4-[2-(  
(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-  
yl}propanamide hydrochloride

#### 20 Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-(3-amino-3-  
oxopropyl)-1,3-thiazol-4-  
yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
from the compound of Step 4 of Production Example 120 in a  
25 similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.47(9H, s), 1.53(9H, s), 1.57-  
1.67(2H, m), 2.24(3H, s), 2.65-2.76(2H, m), 2.76-2.87(2H, m),  
2.87-2.99(2H, m), 5.37(1H, s), 6.14(1H, s), 6.90(2H, d,  
J=8.4Hz), 7.28(2H, d, J=8.4Hz), 8.88-9.28(1H, brs), 10.12(1H,  
30 s), 11.58(1H, s).

MS: 575.0(M+H)<sup>+</sup>, 597.3(M+Na)<sup>+</sup>

#### Step 2

The title compound was prepared from the compound of Step

1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.10(3H, s), 2.23(2H, t, J=7.3Hz), 2.71-2.83(4H, m), 2.83-2.91(2H, m), 6.81(1H, s), 7.14(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 7.31(1H, s), 7.35(4H, s), 9.70(1H, s), 11.94(1H, s).

MS: 375.2 (M+H)<sup>+</sup>, 397.0 (M+Na)<sup>+</sup> free

**Production Example 123:** Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-N,N-dimethyl-4-piperidinecarboxamide dihydrochloride

Step 1

1-[(2-(Acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-4-piperidinecarboxylic acid was prepared from ethyl 1-[(2-(acetylamino)-4-{2-[4-({(Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl}amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-4-piperidinecarboxylate in a similar manner according to Step 1 of Production Example 42.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.51(9H, s), 1.76-2.49(10H, m), 2.69-3.00(6H, m), 3.71(2H, s), 7.04(2H, d, J=8.5Hz), 7.42(2H, d, J=8.5Hz), 10.23(1H, s), 11.13-12.07(1H, brs).

MS: 645.3 (M+H)<sup>+</sup>, 667.2 (M+Na)<sup>+</sup>

Step 2

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[(dimethylamino)carbonyl]-1-piperidinyl)methyl}-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 1 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50(9H, s), 1.54(9H, s), 1.75-

1.89 (2H, m), 1.92-2.03 (2H, m), 2.22 (3H, s), 2.37-2.49 (1H, m), 2.80-2.95 (9H, m), 3.02 (3H, s), 3.43 (2H, s), 7.08 (2H, d, J=8.4Hz), 7.46 (2H, d, J=8.4Hz), 8.61-9.19 (1H, brs), 10.24 (1H, s), 11.63 (1H, s).

<sup>5</sup> MS: 672.2 (M+H)<sup>+</sup>, 694.3 (M+Na)<sup>+</sup>

### Step 3

The title compound was prepared from the compound of Step 2 in a similar manner according to Step 4 of Production Example 31.

<sup>10</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.71-2.01 (4H, m), 2.16 (3H, s), 2.76-2.87 (4H, m), 2.87-3.1 (9H, m), 3.3-3.4 (2H, m), 4.32-4.45 (2H, m), 7.15 (2H, d, J=4.2Hz), 7.31 (2H, d, J=4.2Hz), 7.41 (4H, s), 9.83-9.93 (1H, m), 9.99-10.19 (1H, m), 12.32-12.37 (1H, m).

MS: 472.3 (M+H)<sup>+</sup>, 494.0 (M+Na)<sup>+</sup> free

<sup>15</sup> Production Example 124: Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-N-methyl-4-piperidinecarboxamide dihydrochloride  
Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({4-[  
<sup>20</sup> [(methylamino) carbonyl]-1-piperidinyl)methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 1 of Production Example 123 in a similar manner according to Step 1 of Production Example 32.

<sup>25</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.5 (9H, s), 1.54 (9H, s), 1.65-1.74 (2H, m), 1.75-1.84 (2H, m), 1.87-1.98 (2H, m), 2-2.11 (1H, m), 2.22 (3H, s), 2.8 (3H, d, J=4.8Hz), 2.82-2.91 (6H, m), 3.39 (2H, s), 5.5 (1H, d, J=4.4Hz), 7.07 (2H, d, J=8.4Hz), 7.45 (2H, d, J=8.4Hz), 8.72-8.99 (1H, brs), 10.23 (1H, s), 11.62 (1H, s).

MS: 658.3 (M+H)<sup>+</sup>, 680.3 (M+Na)<sup>+</sup>

### <sup>30</sup> Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.71-2.04 (4H, m), 2.16 (3H, s), 2.25-2.37 (1H, m), 2.54-2.61 (3H, m), 2.82-2.94 (2H, m), 2.96 (4H, s), 3.27-3.37 (2H, m), 4.31-4.44 (2H, m), 7.15 (2H, d, J=8.4Hz), 7.30 (2H, d, J=8.4Hz), 7.41 (4H, s), 7.89-8.00 (1H, m), 9.83-10.16 (2H, m).

MS: 458.2 (M+H)<sup>+</sup>, 480.0 (M+Na)<sup>+</sup> free

**Production Example 125:** Synthesis of 1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-4-piperidinecarboxamide dihydrochloride

Step 1

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-{[4-(aminocarbonyl)-1-piperidinyl]methyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 1 of Production Example 123 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50 (9H, s), 1.53 (9H, s), 1.66-1.75 (2H, m), 1.78-1.87 (2H, m), 1.88-1.99 (2H, m), 2.07-2.17 (1H, m), 2.23 (3H, s), 2.77-2.92 (6H, m), 3.39 (2H, s), 5.5 (2H, s), 7.06 (2H, d, J=8.4Hz), 7.45 (2H, d, J=8.4Hz), 8.94-9.25 (1H, brs), 10.23 (1H, s), 11.61 (1H, s).

MS: 644.2 (M+H)<sup>+</sup>, 666.3 (M+Na)<sup>+</sup>

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.68-2.08 (4H, m), 2.16 (3H, s), 2.25-2.36 (1H, m), 2.82-3.09 (6H, m), 3.27-3.44 (2H, m), 4.30-4.45 (2H, m), 6.87-7.06 (1H, m), 7.15 (2H, d, J=8.4Hz), 7.30 (2H, d, J=8.3Hz), 7.36-7.52 (5H, m), 9.87-10.25 (2H, m), 12.30-12.37 (1H, m).

MS: 444.2 (M+H)<sup>+</sup>, 466.2 (M+Na)<sup>+</sup> free

**Production Example 126:** Synthesis of (3R)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-

5-yl)methyl)-N,N-dimethyl-3-piperidinecarboxamide  
dihydrochloride

Step 1

Ethyl (3R)-1-((2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl)methyl)-3-piperidinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67..

MS: 459.20 (M+H)<sup>+</sup>

Step 2

Ethyl (3R)-1-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl)amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.22 (3H, t, J=7.2Hz), 1.31-1.78 (21H, m), 1.79-2.06 (2H, m), 2.07-2.18 (1H, m), 2.22 (3H, s), 2.43-2.62 (1H, m), 2.62-2.75 (1H, m), 2.84 (4H, s), 2.88-3.01 (1H, m), 3.42 (2H, s), 4.11 (2H, q, J=7.1Hz), 7.08 (2H, d, J=8.4Hz), 7.46 (2H, d, J=8.4Hz), 8.76-9.16 (1H, brs), 10.24 (1H, s), 11.64 (1H, s).

MS: 673.3 (M+H)<sup>+</sup>, 695.2 (M+Na)<sup>+</sup>

Step 3

(3R)-1-[(2-(Acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl)amino)phenyl]ethyl}-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylic acid was prepared from the compound of Step 2 in a similar manner according to Step 1 of Production Example 42.

MS: 645.37 (M+H)<sup>+</sup>

Step 4

Di-tert-butyl {(Z)-[4-{2-[2-(acetylamino)-5-((3R)-3-

[(dimethylamino)carbonyl]-1-piperidinyl)methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 in a similar manner according to Step 1 of Production Example 32.

- 5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.39-1.57(20H, m), 1.66-1.73(1H, m), 1.74-1.83(1H, m), 1.87-1.98(1H, m), 2.08-2.19(1H, m), 2.22(3H, s), 2.72-2.94(10H, m), 3.02(3H, s), 3.41(2H, s), 7.08(2H, d, J=8.4Hz), 7.46(2H, d, J=8.4Hz), 8.70-9.02(1H, brs), 10.24(1H, s), 11.63(1H, s).
- 10 MS: 672.41 (M+H)<sup>+</sup>

#### Step 5

The title compound was prepared from the compound of Step 4 in a similar manner according to Step 4 of Production Example 31.

- 15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.29-1.94(4H, m), 2.16(3H, s), 2.77-3.33(15H, m), 4.27-4.46(2H, m), 7.16(2H, d, J=8.3Hz), 7.27-7.35(2H, m), 7.36-7.48(4H, m), 9.8-9.98(1H, m), 10.22-10.51(1H, brs), 12.29-12.36(1H, m).
- MS: 472.3 (M+H)<sup>+</sup>, 494.2 (M+Na)<sup>+</sup> free

- 20 Production Example 127: Synthesis of (3R)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl)-N-methyl-3-piperidinecarboxamide dihydrochloride
- Step 1

- Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-({(3R)-3-  
25 [(methylamino)carbonyl]-1-piperidinyl)methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 of Production Example 126 in a similar manner according to Step 1 of Production Example 32.
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.50(9H, s), 1.52-1.72(12H, m), 1.84-  
30 1.98(1H, m), 2.01-2.14(1H, m), 2.14-2.23(1H, m), 2.24(3H, s), 2.43-2.51(1H, m), 2.64-2.76(1H, m), 2.76-2.94(8H, m), 3.32(1H, d, J=14Hz), 3.41(1H, d, J=14Hz), 7.06(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz), 7.53(1H, brs), 8.84(1H, brs), 10.24(1H,

s), 11.63(1H, s).

MS: 658.39(M+H)<sup>+</sup>

### Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.31-1.94(4H, m), 2.16(3H, s), 2.54-3.36(12H, m), 4.27-4.48(2H, m), 7.12-7.19(2H, m), 7.25-7.35(2H, m), 7.35(4H, brs), 8.05-8.37(1H, m), 9.79-9.92(1H, m), 10.16-10.42(1H, brs), 12.29-12.37(1H, m).

MS: 458.2(M+H)<sup>+</sup>, 480.1(M+Na)<sup>+</sup> free

**Production Example 128:** Synthesis of (3S)-1-({2-(acetylamino)-4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl}-N,N-dimethyl-3-piperidinecarboxamide dihydrochloride

### Step 1

Ethyl (3S)-1-({2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl)methyl}-3-piperidinecarboxylate was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

MS: 459.21(M+H)<sup>+</sup>

### Step 2

Ethyl (3S)-1-[(2-(acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl]amino}phenyl)ethyl)-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylate was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 68.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.22(3H, t, J=7.2Hz), 1.3-1.79(21H, m), 1.8-2.06(2H, m), 2.08-2.18(1H, m), 2.22(3H, s), 2.43-2.62(1H, m), 2.62-2.75(1H, m), 2.84(4H, s), 2.88-3.01(1H, m), 3.42(2H, s), 4.11(2H, q, J=7.1Hz), 7.08(2H, d, J=8.4Hz),

7.46(2H, d, J=8.4Hz), 8.71-9.23(1H, brs), 10.24(1H, s),  
11.64(1H, s).

MS: 673.3(M+H)<sup>+</sup>, 695.2(M+Na)<sup>+</sup>

### Step 3

5 (3S)-1-[(2-(Acetylamino)-4-{2-[4-((Z)-[(tert-butoxycarbonyl)amino] [(tert-butoxycarbonyl)imino]methyl)amino]phenyl}ethyl)-1,3-thiazol-5-yl)methyl]-3-piperidinecarboxylic acid was prepared from the compound of Step 2 in a similar manner according to Step 1 of  
10 Production Example 42.

MS: 645.36(M+H)<sup>+</sup>

### Step 4

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-((3S)-3-[(dimethylamino)carbonyl]-1-piperidinyl)methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared  
15 from the compound of Step 3 in a similar manner according to Step 1 of Production Example 32.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.4-1.64(20H, m), 1.65-1.73(1H, m), 1.73-1.82(1H, m), 1.86-1.97(1H, m), 2.08-2.18(1H, m), 2.22(3H, s), 2.7-2.93(10H, m), 3.02(3H, s), 3.41(2H, s), 7.08(2H, d, J=8.4Hz), 7.46(2H, d, J=8.3Hz), 8.61-8.99(1H, brs), 10.24(1H, s), 11.63(1H, s).

MS: 672.39(M+H)<sup>+</sup>

### Step 5

25 The title compound was prepared from the compound of Step 4 in a similar manner according to Step 4 of Production Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.29-1.93(4H, m), 2.16(3H, s), 2.77-3.35(15H, m), 4.27-4.45(2H, m), 7.16(2H, d, J=8.4Hz), 7.28-7.35(2H, m), 7.35-7.47(4H, m), 9.8-9.96(1H, m), 10.21-10.46(1H, brs), 12.29-12.36(1H, m).

MS: 472.3(M+H)<sup>+</sup>, 494.2(M+Na)<sup>+</sup> free

Production Example 129: Synthesis of (3S)-1-((2-(acetylamino)-

4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl)-N-methyl-3-piperidinecarboxamide dihydrochloride  
Step 1

Di-tert-butyl {(Z)-[(4-{2-[2-(acetylamino)-5-((3S)-3-  
5 [(methylamino)carbonyl]-1-piperidinyl)methyl)-1,3-thiazol-4-yl]ethyl}phenyl)amino]methylidene}biscarbamate was prepared from the compound of Step 3 of Production Example 128 in a similar manner according to Step 1 of Production Example 32.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.46-1.72 (21H, m), 1.84-1.97 (1H, m),  
10 1.99-2.14 (1H, m), 2.15-2.22 (1H, m), 2.24 (3H, s), 2.43-2.51 (1H, m), 2.65-2.76 (1H, m), 2.76-2.91 (8H, m), 3.32 (1H, d, J=14Hz), 3.41 (1H, d, J=14Hz), 7.06 (2H, d, J=8.4Hz), 7.45 (2H, d, J=8.4Hz), 7.54 (1H, brs), 8.84-9.02 (1H, brs), 10.24 (1H, s), 11.63 (1H, s).

15 MS: 658.40 (M+H)<sup>+</sup>

Step 2

The title compound was prepared from the compound of Step 1 in a similar manner according to Step 4 of Production Example 31.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.31-1.94 (4H, m), 2.16 (3H, s), 2.53-3.36 (12H, m), 4.24-4.46 (2H, m), 7.12-7.19 (2H, m), 7.25-7.35 (2H, m), 7.36 (4H, brs), 8.06-8.37 (1H, m), 9.83-9.99 (1H, m), 10.28-10.54 (1H, brs), 12.33 (1H, s).

MS: 458.2 (M+H)<sup>+</sup>, 480.2 (M+Na)<sup>+</sup> free

25 Production Example 130: Synthesis of N-{4-[2-(2-amino-1H-benzimidazol-6-yl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide

Step 1

N-{4-[2-(3,4-Dinitrophenyl)vinyl]-5-[4-(methylthio)benzyl]-1,3-thiazol-2-yl}acetamide was prepared  
30 from 2-(acetylamino)-5-[4-(methylthio)benzyl]-1,3-thiazole-4-carbaldehyde in a similar manner according to Step 5 of Production Example 45.

Z : E = 3 : 1

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.08 (3Hx3/4, s), 2.12 (3Hx1/4, s), 2.44 (3H, s), 4.13 (2Hx3/4, s), 4.32 (2Hx1/4, s), 6.71 (1Hx3/4, d,  $J=12.5\text{Hz}$ ), 6.97 (1Hx3/4, d,  $J=12.3\text{Hz}$ ), 7.06-8.61 (7H + 2Hx1/4, m), 11.85 (1Hx3/4, s), 12.18 (1Hx1/4, s).

MS: 471.1 (M+H) $^+$ , 493.9 (M+Na) $^+$

### Step 2

N-{4-[2-(3,4-Diaminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 1 in a similar manner according to Step 2 of Production Example 32 and Step 6 of Production Example 45.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.23 (3H, s), 2.70-2.85 (4H, m), 3.03 (3H, s), 3.88 (2H, s), 6.34 (1H, d,  $J=1.8\text{Hz}$ ), 6.39 (1H, dd,  $J=1.8, 7.8\text{Hz}$ ), 6.56 (1H, d,  $J=7.7\text{Hz}$ ), 7.14 (2H, d,  $J=8.3\text{Hz}$ ), 7.79 (2H, d,  $J=8.4\text{Hz}$ ), 8.30-9.45 (1H, brs).

MS: 445.0 (M+H) $^+$ , 467.0 (M+Na) $^+$

### Step 3

To a suspension of N-{4-[2-(3,4-diaminophenyl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide (70.8 mg) in MeOH (0.7 ml) was added cyanogen bromide (25.3 mg), then the mixture was stirred for 14 h at 20°C. To the reaction mixture was added 1N-NaOH (0.239 ml) and the mixture was concentrated *in vacuo*. To the residue was added  $\text{CHCl}_3$  : MeOH = 10 : 1 (10 ml), and an insoluble material was removed by filtration. The filtrate was purified by flash column chromatography over NH silica gel with  $\text{CHCl}_3$  / MeOH (100:1  $\rightarrow$  10:1) as an eluent to give colorless oil. The oil was solidified with  $\text{CH}_2\text{Cl}_2$  :  $\text{Et}_2\text{O}$  = 2 : 1 to give N-{4-[2-(2-amino-1H-benzimidazol-6-yl)ethyl]-5-[4-(methylsulfonyl)benzyl]-1,3-thiazol-2-yl}acetamide as a white solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.09 (3H, s), 2.85 (4H, s), 3.16 (3H, s), 3.97 (2H, s), 6.01 (2H, s), 6.55-6.77 (1H, m), 6.78-6.90 (1H, m),

6.96(1H, d, J=7.8Hz), 7.10-7.30(2H, brs), 7.72(2H, d, J=8.1Hz), 10.55(1H, d, J=10.5Hz), 11.50-12.20(1H, brs).

MS: 470.2(M+H)<sup>+</sup>, 492.1(M+Na)<sup>+</sup>

**Production Example 131:** Synthesis of N-{4-[2-(2-amino-1H-  
5 benzimidazol-6-yl)ethyl]-1,3-thiazol-2-yl}acetamide

Step 1

N-{4-[2-(3,4-Dinitrophenyl)vinyl]-1,3-thiazol-2-  
yl}acetamide was prepared from 2-(acetylamino)-1,3-thiazole-4-  
carbaldehyde in a similar manner according to Step 5 of  
10 Production Example 1.

Z : E = 8 : 1

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 2.13(3Hx8/9, s), 2.17(3Hx1/9, s),  
6.64(1Hx8/9, d, J=12.6Hz), 6.80(1Hx8/9, d, J=12.6Hz),  
7.29(1Hx1/9, d, J=15.7Hz), 7.33(1Hx8/9, s), 7.39(1Hx1/9, s),  
15 7.63(1Hx1/9, d, J=15.7Hz), 8.00-8.50(3H, m), 11.97(1Hx8/9, s),  
12.30(1Hx1/9, s).

MS: 335.0(M+H)<sup>+</sup>, 357.1(M+Na)<sup>+</sup>

Step 2

N-{4-[2-(3,4-Diaminophenyl)ethyl]-1,3-thiazol-2-  
20 yl}acetamide was prepared from the compound of Step 1 in a  
similar manner according to Step 6 of Production Example 1.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.22(3H, s), 2.58-3.17(8H, m), 6.46-  
6.56(3H, m), 6.62(1H, d, J=8.3Hz), 8.84-10.42(1H, brs).

MS: 277.1(M+H)<sup>+</sup>, 299.2(M+Na)<sup>+</sup>

25 Step 3

The title compound was prepared from the compound of Step  
2 in a similar manner according to Step 3 of Production  
Example 130.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.11(3H, s), 2.79-2.97(4H, m), 6(2H,  
30 s), 6.59-6.8(2H, m), 6.91(1H, s), 6.97(1H, d, J=7.9Hz), 10.34-  
10.73(1H, brs), 11.94-12.22(1H, brs).

MS: 302.2(M+H)<sup>+</sup>, 324.1(M+Na)<sup>+</sup>

**Production Example 132:** Synthesis of N-({2-(acetylamino)-4-[2-

(4-{[amino(imino)methyl]amino}phenyl)ethyl]-1,3-thiazol-5-yl)methyl)-N-methylacetamide hydrochloride

### Step 1

N-{5-[(Methylamino)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide was prepared from N-{4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide in a similar manner according to Step 1 of Production Example 67.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.05 (3H, s), 2.46 (3H, s), 3.75 (2H, s), 6.67 (2H, s), 7.41 (2H, d, J=8.9Hz), 8.01 (2H, d, J=8.8Hz), 9.7-11.69 (1H, brs).

MS: 333.1 (M+H)<sup>+</sup>, 355.1 (M+Na)<sup>+</sup>

### Step 2

To a suspension of N-{5-[(methylamino)methyl]-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-2-yl}acetamide (46.8 mg) in dichloromethane (0.5 ml) were added N,N-diisopropylethylamine (27 μl) and acetyl chloride (10 μl), and the mixture was stirred for 2 h at 20°C. To the reaction mixture were added dichloromethane (5 ml), N,N-diisopropylethylamine (27 μl) and acetyl chloride (10 μl), and the mixture was stirred for 5 min. at 20°C, then washed with saturated sodium hydrogen carbonate aqueous solution (5 ml) and brine (5 ml), dried over MgSO<sub>4</sub>, filtered and evaporated to give a yellow solid (67.8 mg). The crude compound was purified by preparative silica gel thin-layer chromatography with chloroform / methanol (20:1) as an eluent to give N-{2-(acetylamino)-4-[(Z)-2-(4-nitrophenyl)vinyl]-1,3-thiazol-5-yl)methyl)-N-methylacetamide as a yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 2.12 (3Hx2/3, s), 2.13 (3Hx1/3, s), 2.14 (3Hx2/3, s), 2.24 (3Hx1/3, s), 3.02 (3Hx2/3, s), 3.05 (3Hx1/3, s), 4.62 (2Hx2/3, s), 4.79 (2Hx1/3, s), 6.61 (1Hx1/3, d, J=12.6Hz), 6.70 (1Hx2/3, d, J=12.6Hz), 6.77 (1Hx1/3, d, J=12.6Hz), 6.82 (1Hx2/3, d, J=12.6Hz),

7.43(2Hx2/3, d, J=8.8Hz), 7.65(2Hx1/3, d, J=8.8Hz),  
8.06(2Hx2/3, d, J=8.8Hz), 8.22(2Hx1/3, d, J=8.8Hz), 9.09-  
9.26(1Hx1/3, brs), 9.26-9.51(1Hx2/3, brs).

MS: 375.2 (M+H)<sup>+</sup>, 397.1 (M+Na)<sup>+</sup>

<sup>5</sup> Step 3

N-({2-(Acetylamino)-4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-5-yl)methyl)-N-methylacetamide was prepared from the compound of Step 2 in a similar manner according to Step 6 of Production Example 45.

<sup>10</sup> MS: 347.25 (M+H)<sup>+</sup>

Step 4

Di-tert-butyl [(Z)-({4-[2-(2-(acetylamino)-5-  
{[acetyl(methyl)amino]methyl}-1,3-thiazol-4-  
yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared  
<sup>15</sup> from the compound of Step 3 in a similar manner according to  
Step 3 of Production Example 31.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s), 2.06(3Hx3/4,  
s), 2.12(3Hx1/4, s), 2.23(3H, s), 2.77(3Hx1/4, s),  
2.81(3Hx3/4, s), 2.90(4H, s), 4.20(2Hx1/4, s), 4.46(2Hx3/4,  
<sup>20</sup> s), 7.01(2Hx1/4, d, J=8.6Hz), 7.07(2Hx3/4, d, J=8.5Hz),  
7.43(2Hx3/4, d, J=8.5Hz), 7.46(2Hx1/4, d, J=8.0Hz), 8.81-  
9.09(1H, brs), 10.22(1Hx3/4, s), 10.25(1Hx1/4, s), 11.62(1H,  
s).

MS: 589.2 (M+H)<sup>+</sup>, 611.2 (M+Na)<sup>+</sup>

<sup>25</sup> Step 5

The title compound was prepared from the compound of Step  
4 in a similar manner according to Step 4 of Production  
Example 31.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>), δ (ppm): 1.98(3Hx3/4, s), 2.02(3Hx1/4, s),  
<sup>30</sup> 2.11(3Hx3/4, s), 2.12(3Hx1/4, s), 2.60(3Hx1/4, s),  
2.82(3Hx3/4, s), 2.89(4H, s), 4.39(2Hx3/4, s), 4.45(2Hx1/4,  
s), 7.13(2Hx1/4, d, J=8.1Hz), 7.14(2Hx3/4, d, J=8.4Hz),  
7.22(2Hx1/4, d, J=8.4Hz), 7.25(2Hx3/4, d, J=8.4Hz), 7.31(4H,

s), 9.61(1H, s), 12.03(1Hx3/4, s), 12.13(1Hx1/4, s).

MS: 389.19(M+H)<sup>+</sup> free

**Production Example 133:** Synthesis of N-[4-(2-{4-[(2-aminoethyl)amino]phenyl}ethyl)-1,3-thiazol-2-yl]acetamide  
5 dihydrochloride

Step 1

To a suspension of N-{4-[2-(4-aminophenyl)ethyl]-1,3-thiazol-2-yl}acetamide (100 mg) in toluene were added tert-butyl (2-bromoethyl)carbamate (87.5 mg) and N,N-  
10 diisopropylethylamine (52  $\mu$ l), and the mixture was stirred at 80°C for 24 h. The reaction mixture was allowed to cool to room temperature, water (10 ml) was added, and the organic layer was separated, washed with saturated aqueous NaCl, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* to give tert-  
15 butyl {2-[(4-{2-[2-(acetylamino)-1,3-thiazol-4-yl]ethyl}phenyl)amino]ethyl}carbamate as a pale brown amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta$  (ppm): 1.45(9H, s), 2.23(3H, s), 2.86(4H, s), 3.15-3.28(2H, m), 3.15-3.47(2H, m), 4.64-5.02(1H, brs),  
20 6.49(1H, s), 6.52(2H, d, J=8.0Hz), 6.95(2H, d, J=8.0Hz), 9.22-10.10(1H, brs).

MS: 405.2(M+H)<sup>+</sup>, 427.3(M+Na)<sup>+</sup>

Step 2

The title compound was prepared from the compound of Step  
25 2 in a similar manner according to Step 2 of Production Example 10.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>),  $\delta$  (ppm): 2.11(3H, s), 2.81(4H, s), 2.92-3.05(2H, m), 3.29(2H, t, J=6.2Hz), 6.67(2H, d, J=7.7Hz), 7.01(2H, d, J=8.1Hz), 7.87-8.24(3H, brs), 12.08(1H, s).  
30 MS: 305.2(M+H)<sup>+</sup>, 327.2(M+Na)<sup>+</sup>

**Production Example 134:** Synthesis of N-{4-[3-(2-{[amino(imino)methyl]amino}ethyl)phenyl]-1,3-thiazol-2-yl}acetamide hydrochloride

Step 1

To a suspension of lithium aluminium hydride in dry tetrahydrofuran (50 ml) was added (3-bromophenyl)acetic acid (10 g) in tetrahydrofuran (100 ml) under ice cooling. The mixture was refluxed for 2 hours. After cooling, to the reaction mixture were added water and aqueous Rochelle salt. The mixture was stirred for another 30 min. Aqueous layer was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give 2-(3-bromophenyl)ethanol. This compound was used for the next reaction without further purification.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 1.66(1H, brs), 2.84(2H, dd, J=6.5, 14Hz), 3.85(2H, dt, J=6.5, 2.6Hz), 7.13-7.39(4H, m).

Step 2

To a solution of 2-(3-bromophenyl)ethanol (7 g) in N,N-dimethylformamide (100 ml) were added tert-butyldimethylsilyl chloride (5.77 g) and imidazole (2.84 g) at 25°C. The mixture was stirred at 25°C for 12 h. The reaction mixture was poured into water (500 ml) and extracted with ethyl acetate (100 mlx2). The combined organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with mixed solvent of n-hexane and ethyl acetate to give [2-(3-bromophenyl)ethoxy] (tert-butyl)dimethylsilane as colorless oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 0.01(6H, s), 0.88(9H, s), 2.81(2H, dt, J=6.5, 9.5Hz), 3.81(2H, dt, J=3.0, 6.5Hz), 7.14-7.39 (5H, brs).

Step 3

To a solution of 1.6 g of [2-(3-bromophenyl)ethoxy] (tert-butyl)dimethylsilane in tetrahydrofuran (20 ml) was added n-BuLi in hexane (1.57M, 3.88 ml) at -70°C, then the reaction mixture was stirred at same temperature for 30 min. To the

solution was added dimethylacetamide (1.42 ml) drop wise at the same temperature. The mixture was stirred for another 1 hour. To the reaction mixture were added water and 8 ml of 1N HCl under ice-cooling. The mixture was stirred for 1 hour,  
5 then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with n-hexane and ethyl acetate (20/1-10/1) as an eluent to give 1-[3-(2-[[tert-  
10 butyl(dimethyl)silyl]oxy}ethyl)phenyl]ethanone (350 mg) as colorless oil.  
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 0.03(6H, s), 0.85(9H, s), 2.61(3H, s), 2.87(2H, t, J=6.7 Hz), 3.82(2H, t, J=6.7Hz), 7.20-7.24(1H, m), 7.35-7.44(2H, m), 7.77-7.82(2H, m).

15 MS: 279 (M+H)<sup>+</sup>

#### Step 4

To a solution of 1-[3-(2-[[tert-butyl(dimethyl)silyl]oxy}ethyl)phenyl]ethanone (755 mg) in tetrahydrofuran (4 ml) was added bromine (168 ml) drop wise at  
20 0°C. The mixture was stirred at 25°C for 1 h. To the reaction mixture was added aq. saturated NaHCO<sub>3</sub>, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give crude of 2-bromo-1-[3-(2-  
25 hydroxyethyl)phenyl]ethanone as colorless oil. This compound was used for the next reaction without further purification.

#### Step 5

To a solution of 2-bromo-1-[3-(2-hydroxyethyl)phenyl]ethanone (crude, 658 mg) in  
30 tetrahydrofuran (15 ml) was added 1-acetyl-2-thiourea (320 mg) at 25°C. The mixture was stirred at 60°C for 2 h. The residual colorless crystals were collected by filtration. The crystals were washed with isopropyl ether, and dried under reduced

pressure to give N-{4-[3-(2-hydroxyethyl)phenyl]-1,3-thiazol-2-yl}acetamide (514 mg) as a colorless crystal.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 2.76(2H, t, J=6.9Hz), 3.63(2H, t, J=6.9 Hz), 4.89(1H, brs), 7.16(1H, d, J=7.7 Hz), 7.32(1H, dd, J=7.7, 7.6Hz), 7.56(1H, s), 7.70(2H, d, J=7.6 Hz), 7.76(1H, s), 12.24(1H, s).

MS: 263(M+H)<sup>+</sup>

#### Step 6

To a suspension of N-{4-[3-(2-hydroxyethyl)phenyl]-1,3-thiazol-2-yl}acetamide (300 mg) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) were added methansulfonyl chloride (106 μl) and triethylamine (207 μl) at 5°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Resulting residue was purified by silica gel column chromatography with n-hexane and ethyl acetate (1:1) as an eluent to give 2-{3-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl methanesulfonate (388 mg) as a colorless solid.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(3H, s), 3.04(2H, t, J=6.9 Hz), 3.12(3H, s), 4.45(2H, t, J=6.9 Hz), 7.23-7.42(2H, m), 7.60(1H, s), 7.75-7.81(2H, m), 12.26(1H, s).

MS: 341(M+H)<sup>+</sup>

#### Step 7

To a solution of 2-{3-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl methanesulfonate (388 mg) in N,N-dimethylformamide (5 ml) were added di-tert-butyliminodicarboxylate (322 mg) and K<sub>2</sub>CO<sub>3</sub> (236 mg) at 25°C. The mixture was stirred at 80°C for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure.

Resulting colorless oil containing N-{4-(3-[2-{di-(tert-butoxycarbonyl)amino}ethyl]phenyl)-1,3-thiazol-2-yl}acetamide was used for the next reaction without further purification.

#### Step 8

5 N-{4-[3-(2-Aminoethyl)phenyl]-1,3-thiazol-2-yl}acetamide was prepared from the compound of Step 7 in a similar manner according to Step 2 of Production Example 31.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16(1H, s), 2.74(2H, dd, J=6.8, 6.2Hz), 2.88(2H, dd, J=7, 7.8Hz), 7.17(1H, d, J=7.7Hz),  
10 7.35(1H, dd, J=7.7, 8Hz), 7.58(1H, s), 7.73(1H, d, J=8Hz), 7.74(1H, s).

MS: 262 (M+H)<sup>+</sup>

#### Step 9

15 Di-tert-butyl {(Z)-[(2-{3-[2-(acetylamino)-1,3-thiazol-4-yl]phenyl}ethyl)amino]methylidene}biscarbamate was prepared from the compound of Step 8 in a similar manner according to Step 5 of Production Example 18.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 1.45(9H, s), 1.50(3H, s), 2.27(3H, s), 2.92(2H, t, J=7.5Hz), 3.71(2H, dt, J=7.5, 7.2Hz),  
20 7.11-7.41(4H, d), 7.65-7.78(1H, m).

MS: 504 (M+H)<sup>+</sup>

#### Step 10

The title compound was prepared from the compound of Step 9 in a similar manner according to Step 4 of Production  
25 Example 31.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 2.16(3H, s), 2.83(2H, t, J=6.9Hz), 3.41(2H, m), 7.23(1H, d, J=7.7Hz), 7.38(1H, dd, J=7.7, 7.8 Hz), 7.52(1H, t, J=5.5Hz), 7.59(1H, s), 7.75(1H, d, J=8.1Hz), 7.79(1H, s), 12.23(1H, s).  
30 MS: 304 (M+H)<sup>+</sup> free

**Production Example 135:** Synthesis of N-(4-[2-(4-{[amino(imino)methyl]amino}phenyl)ethyl]-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide

hydrochloride

Step 1

tert-Butyl N-{4-[2-(2-(acetylamino)-5-{(E)-2-[4-(methylsulfonyl)phenyl]vinyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from 2-(acetylamino)-4-{2-[4-(tert-butoxycarbonylamino)phenyl]ethyl}-1,3-thiazole-5-carbaldehyde in a similar manner according to Step 5 of Production Example 45.

MS: 542 (M+H)<sup>+</sup> free

Step 2

tert-Butyl N-{4-[2-(2-(acetylamino)-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-4-yl)ethyl]phenyl}carbamate was prepared from the compound of Step 1 in a similar manner according to Step 6 of Production Example 45.

MS: 544 (M+H)<sup>+</sup>

Step 3

N-(4-[2-(4-Aminophenyl)ethyl]-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-2-yl)acetamide was prepared from the compound of Step 2 in a similar manner according to Step 2 of Production Example 31.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 2.23(3H, s), 2.61(4H, s), 2.78(4H, s), 2.98(3H, s), 3.55(2H, brs), 6.57(2H, d, J=8.5Hz), 6.81(2H, d, J=8.5Hz), 7.25(2H, d, J=8.5Hz), 7.82(2H, d, J=8.5Hz), 8.80(1H, s).

MS: 444 (M+H)<sup>+</sup>

Step 4

Di-tert-butyl [(E)-({4-[2-(2-(acetylamino)-5-{2-[4-(methylsulfonyl)phenyl]ethyl}-1,3-thiazol-4-yl)ethyl]phenyl}amino)methylidene]biscarbamate was prepared from the compound of Step 3 in a similar manner according to Step 5 of Production Example 18.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>), δ (ppm): 1.49(9H, s), 1.53(9H, s),

2.22 (3H, s), 2.59-2.73 (4H, m), 2.84 (4H, s), 2.98 (3H, s),  
6.99 (2H, d, J=8.4Hz), 7.28 (2H, d, J=8.4Hz), 7.44 (2H, d,  
J=8.4Hz), 7.83 (2H, d, J=8.4Hz), 8.99 (1H, bra), 10.23 (1H, s),  
11.62 (1H, s).

5 MS: 686 (M+H)<sup>+</sup>

Step 5

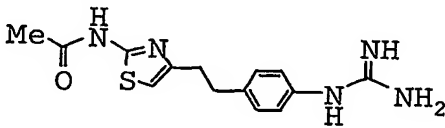
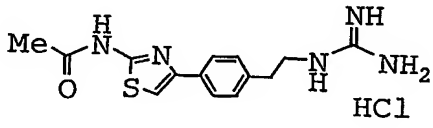
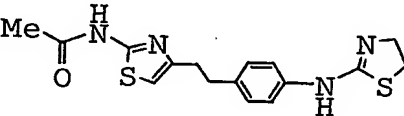
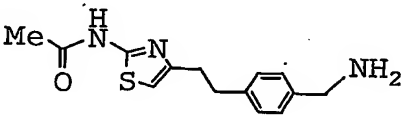
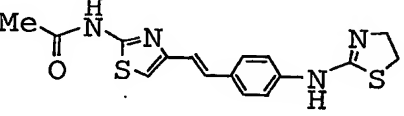
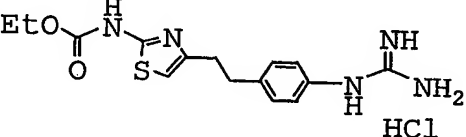
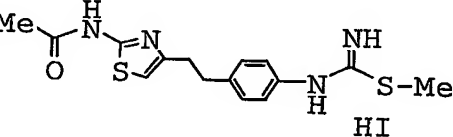
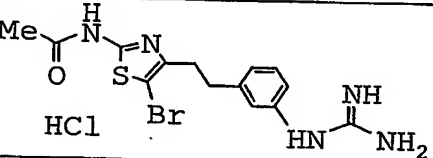
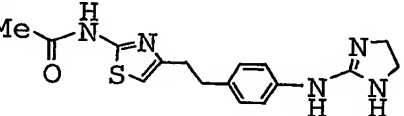
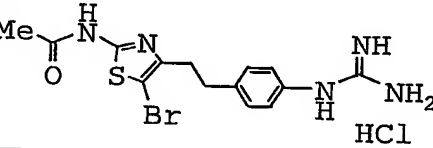
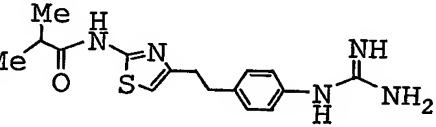
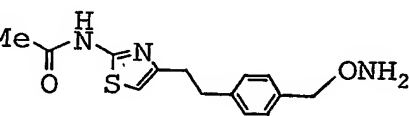
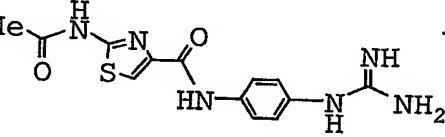
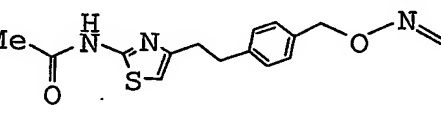
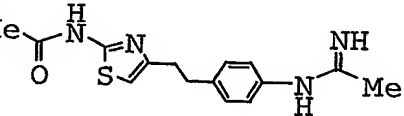
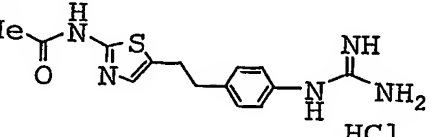
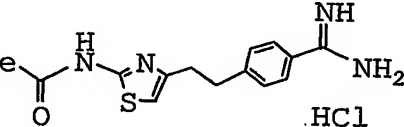
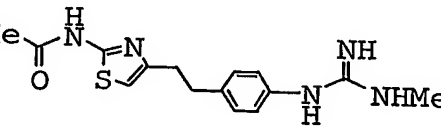
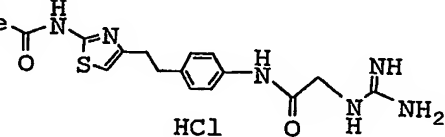
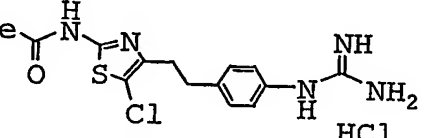
The title compound was prepared from the compound of Step  
4 in a similar manner according to Step 4 of Production  
Example 31.

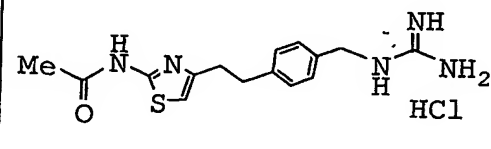
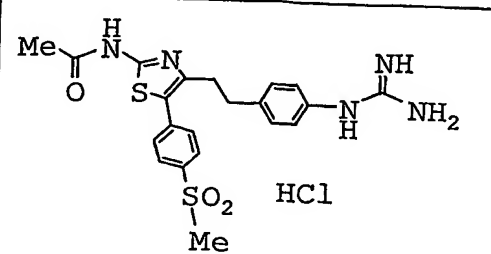
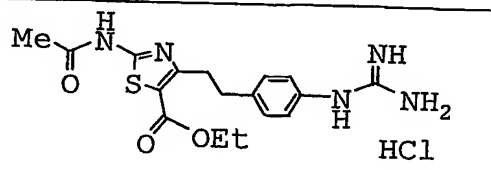
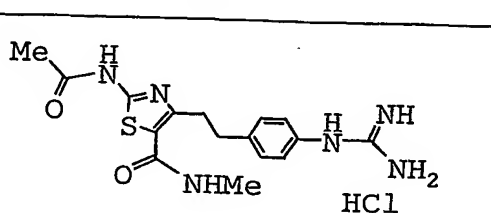
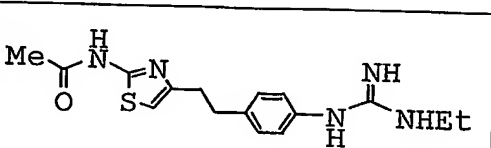
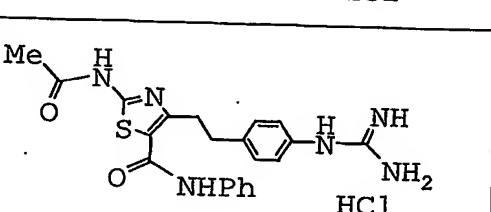
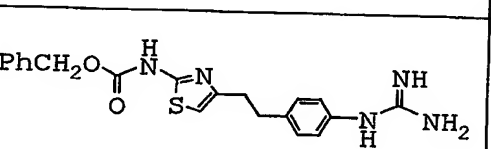
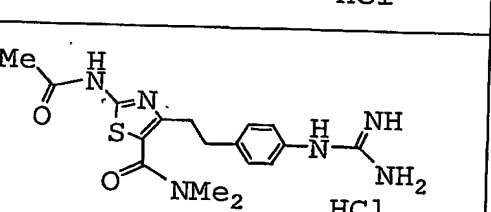
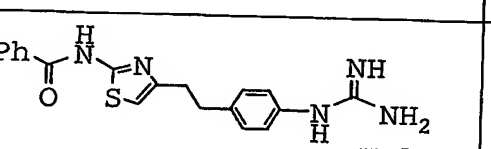
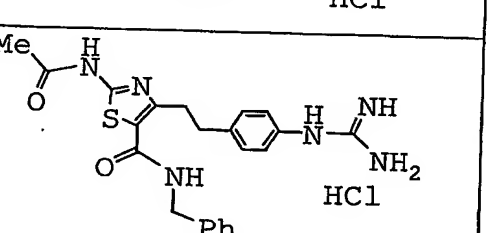
10 <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>), δ (ppm): 2.16 (3H, s), 2.67 (4H, brs),  
2.82-2.94 (4H, m), 3.14 (3H, s), 7.12 (2H, d, J=8.4Hz), 7.20 (2H,  
d, J=8.4Hz), 7.43 (2H, d, J=8.4Hz), 7.82 (2H, d, J=8.4Hz),  
9.87 (1H, s), 11.97 (1H, s).

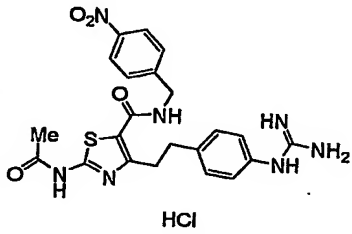
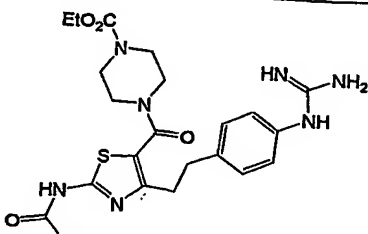
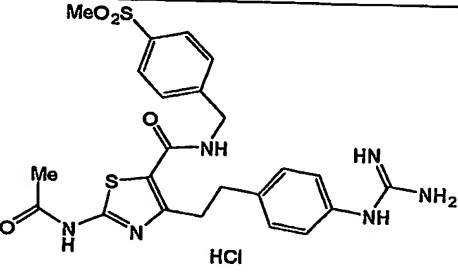
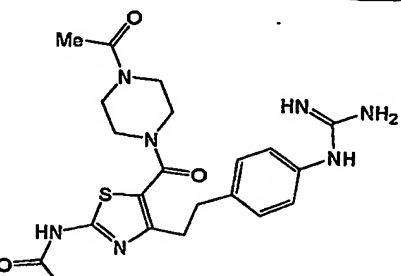
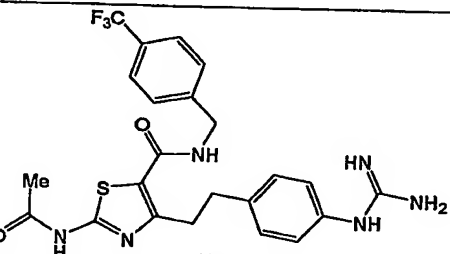
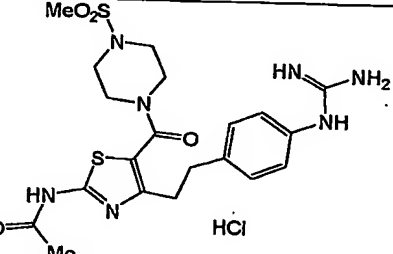
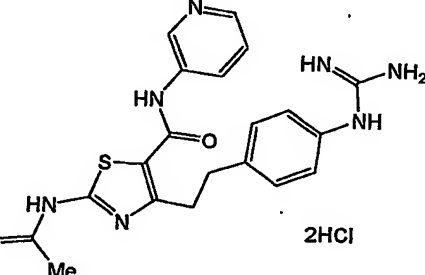
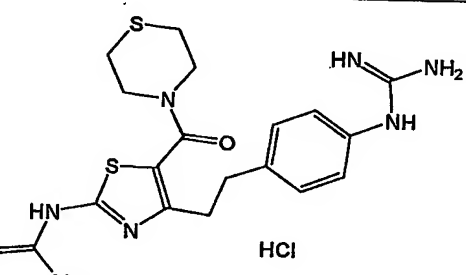
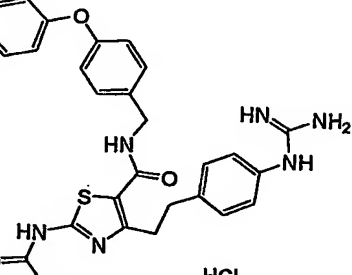
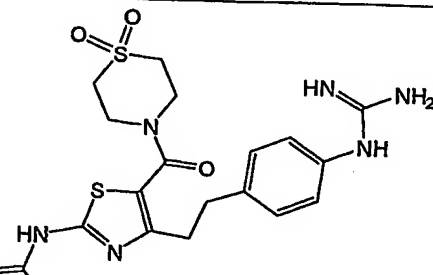
MS: 486 (M+H)<sup>+</sup>

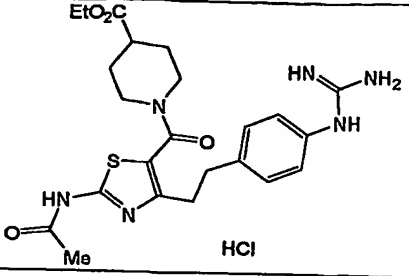
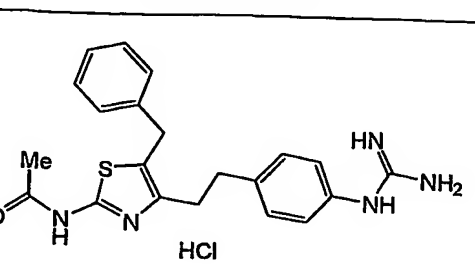
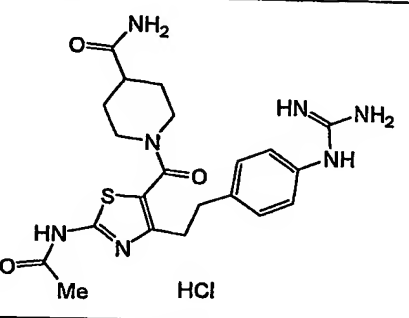
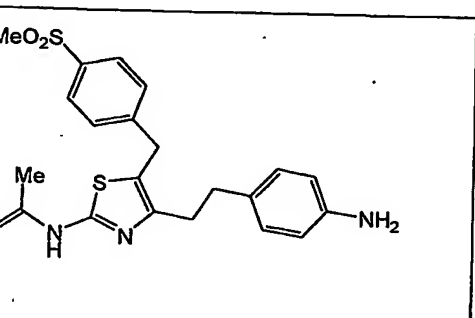
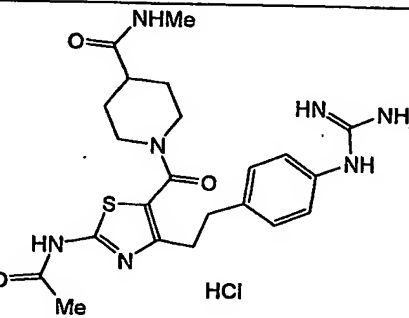
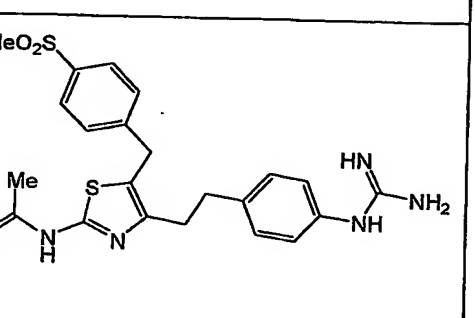
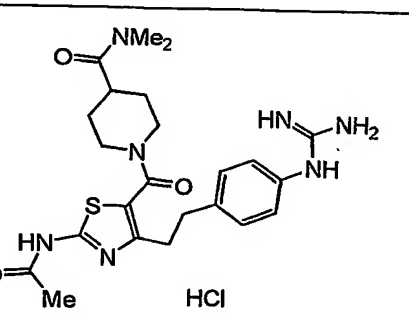
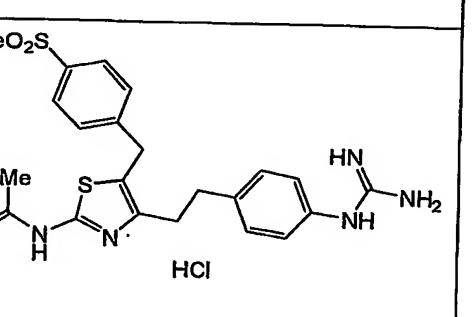
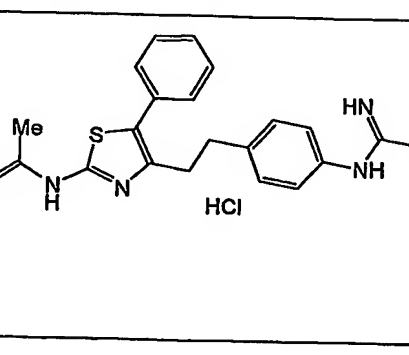
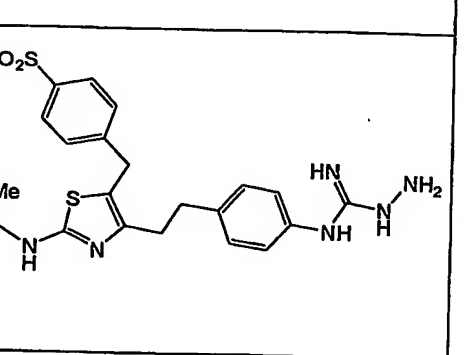
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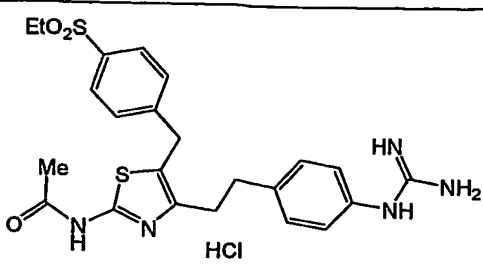
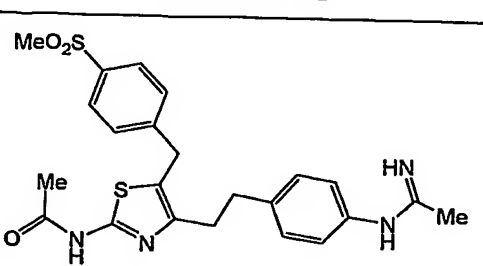
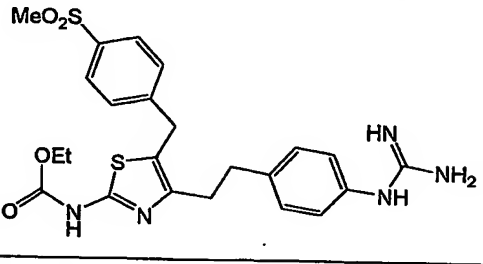
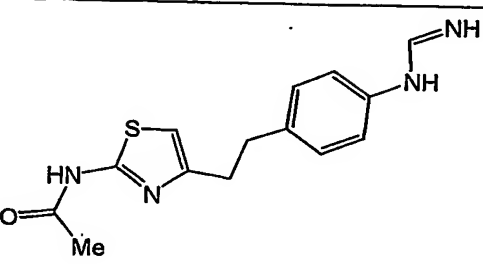
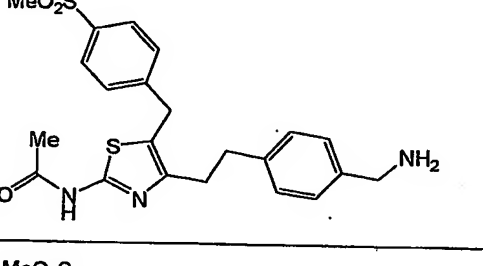
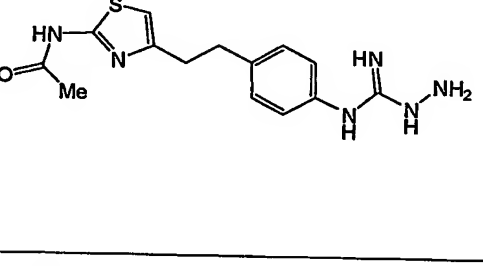
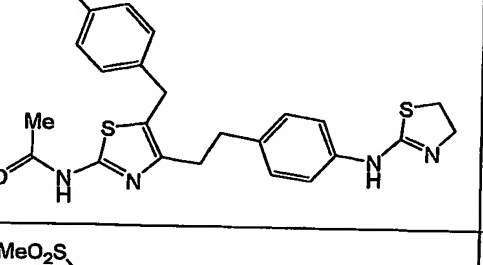
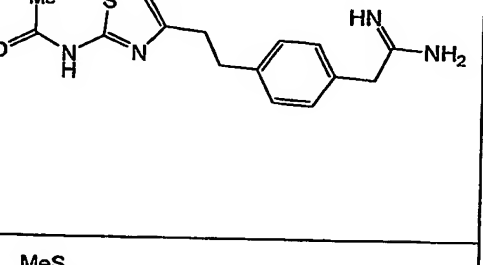
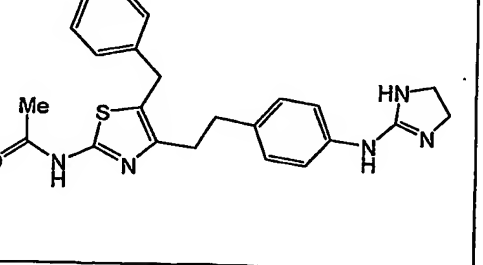
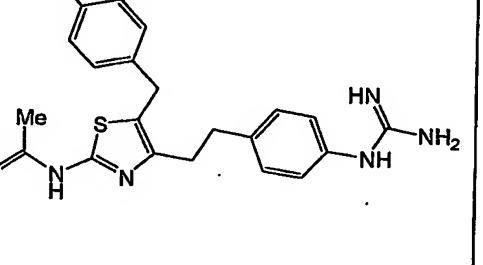
The compounds according to the present invention useful  
as VAP-1 inhibitors are listed in the following tables.

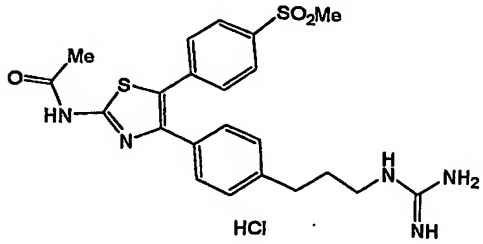
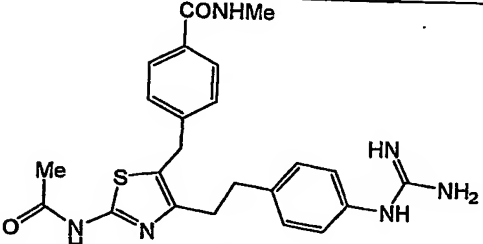
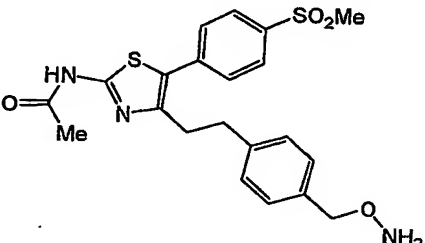
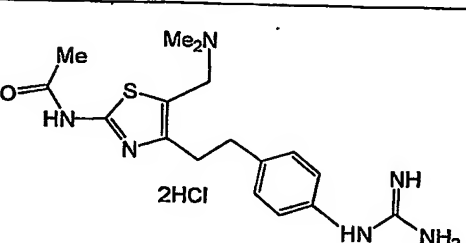
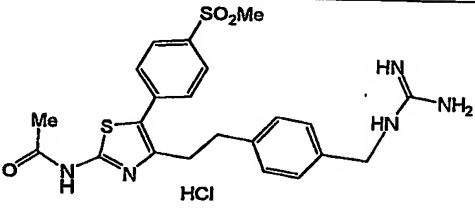
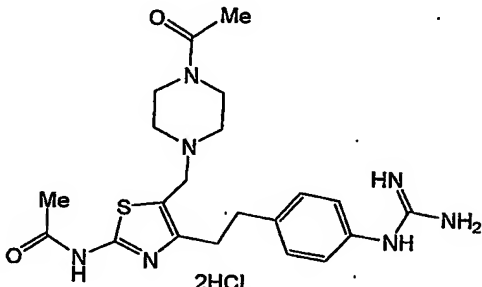
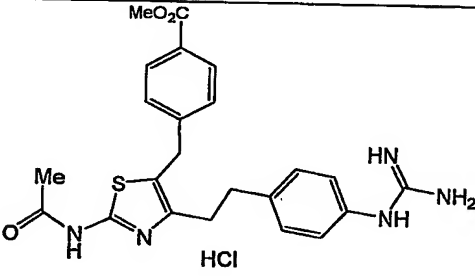
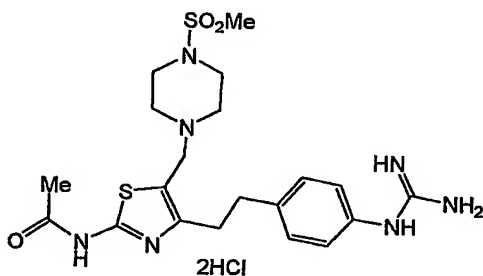
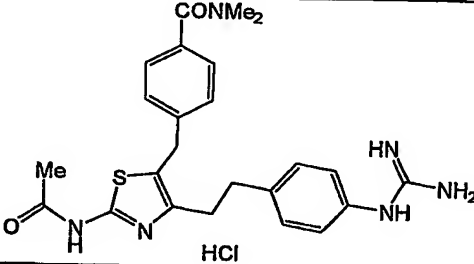
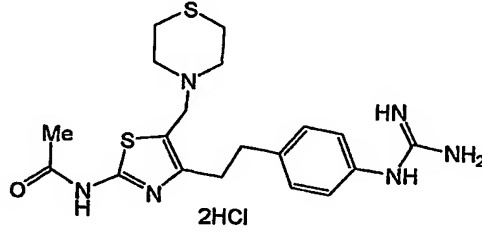
No.	Structure	No.	Structure
1	 <p>Compound A</p>	11	 <p>HCl</p>
2		12	
3		13	 <p>HCl</p>
4	 <p>HI</p>	14	 <p>HCl</p>
5		15	 <p>HCl</p>
6	 <p>HCl</p>	16	
7		17	
8		18	 <p>HCl</p>
9	 <p>HCl</p>	19	
10	 <p>HCl</p>	20	 <p>HCl</p>

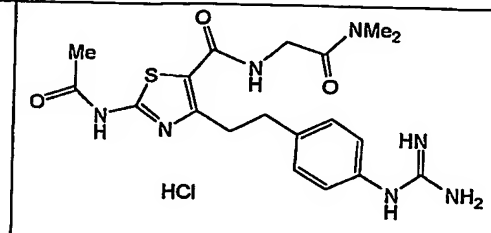
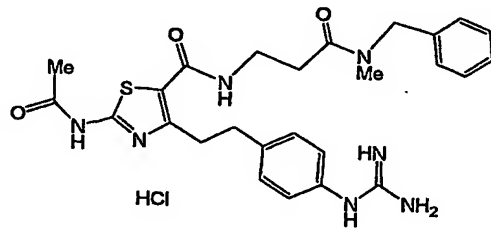
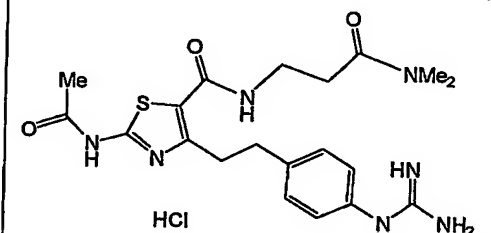
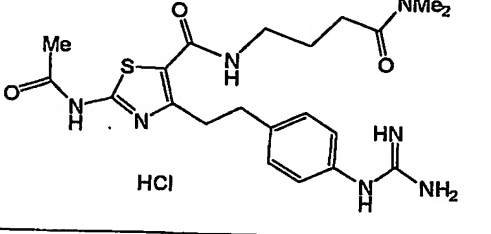
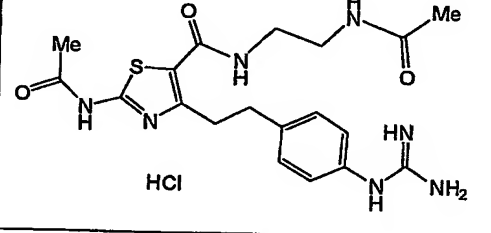
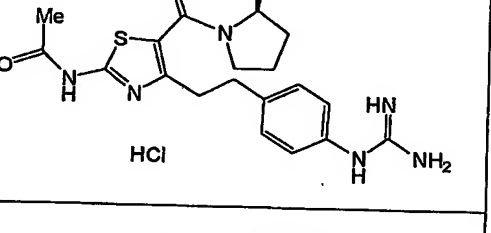
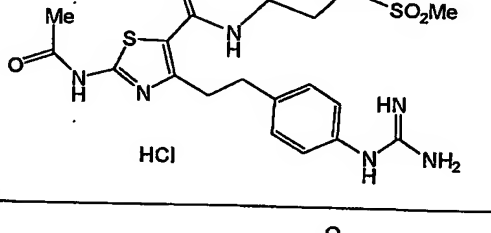
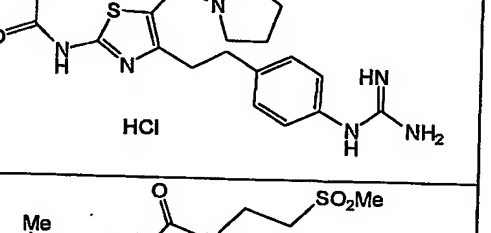
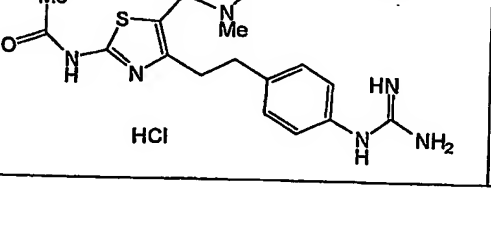
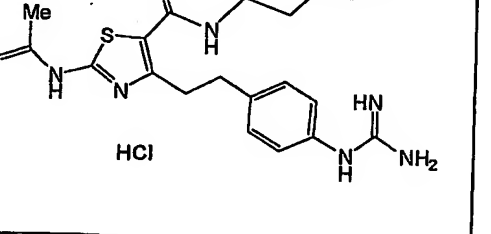
No.	Structure	No.	Structure
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22		27	
23		28	
24		29	
25		30	

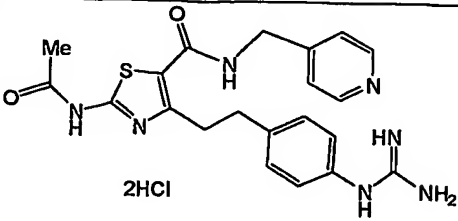
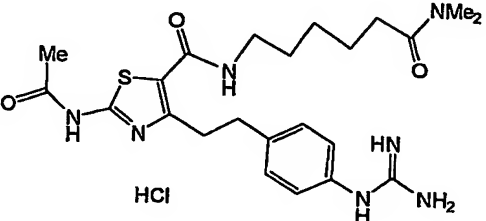
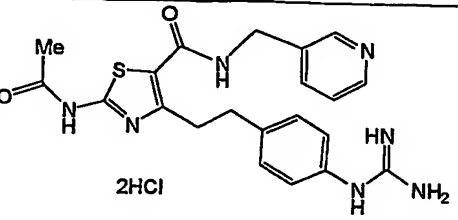
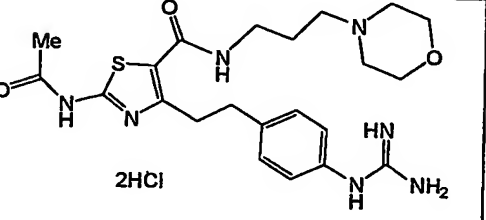
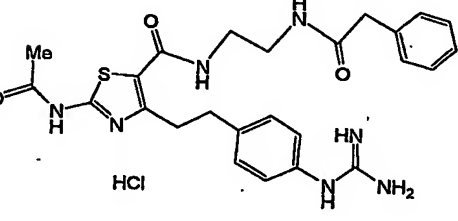
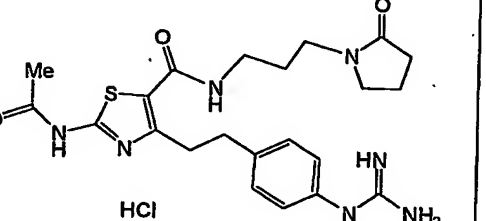
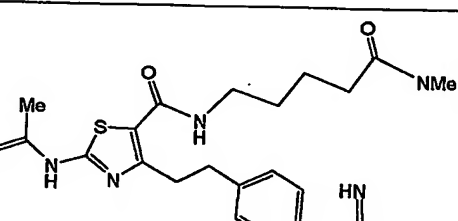
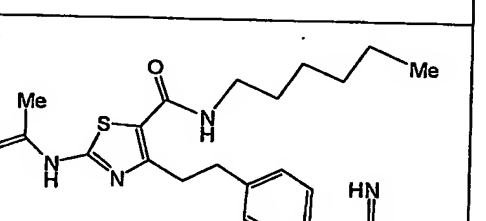
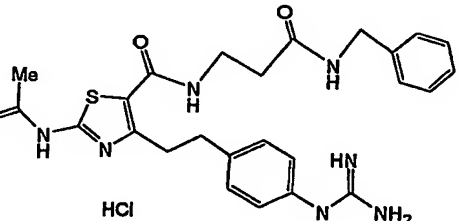
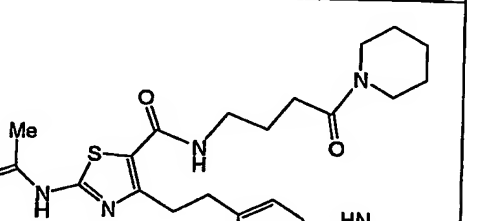
No.	Structure	No.	Structure
31	 <p>HCl</p>	36	 <p>HCl</p>
32	 <p>HCl</p>	37	 <p>HCl</p>
33	 <p>HCl</p>	38	 <p>HCl</p>
34	 <p>2HCl</p>	39	 <p>HCl</p>
35	 <p>HCl</p>	40	 <p>HCl</p>

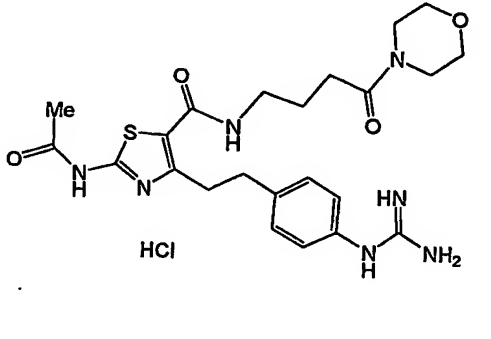
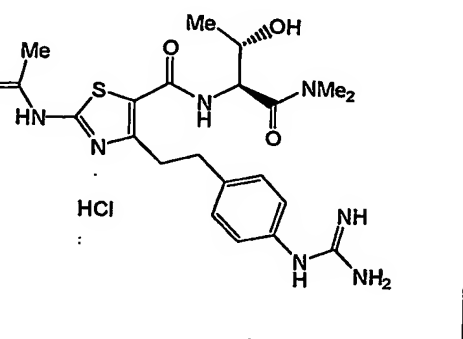
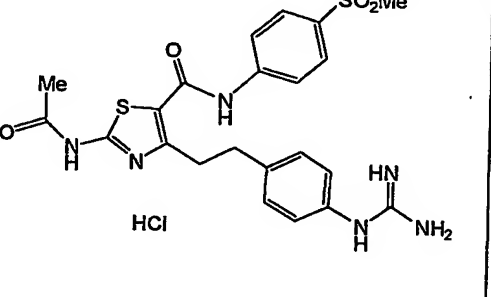
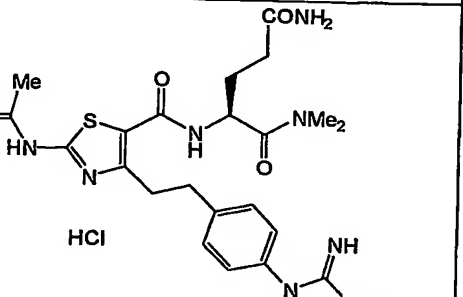
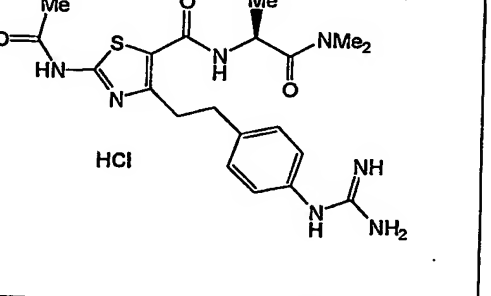
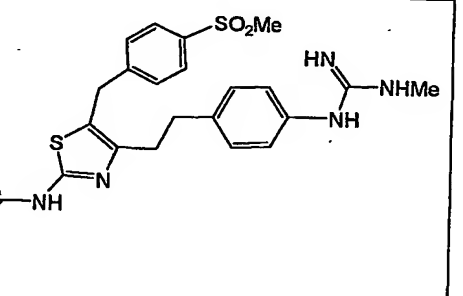
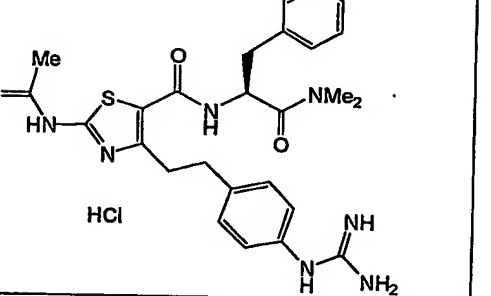
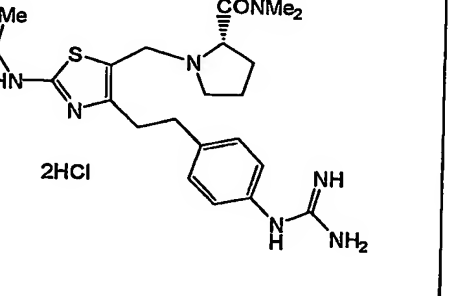
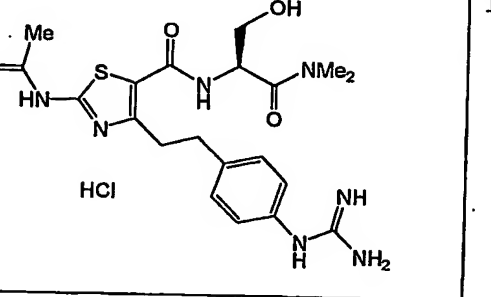
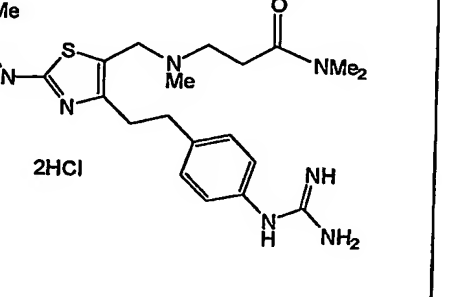
No.	Structure	No.	Structure
41		46	
42		47	
43		48	
44		49	
45		50	

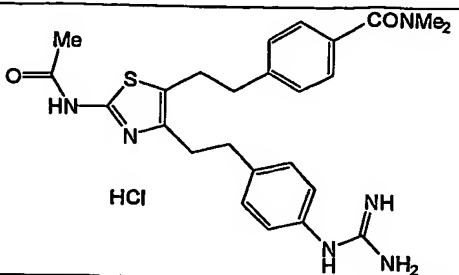
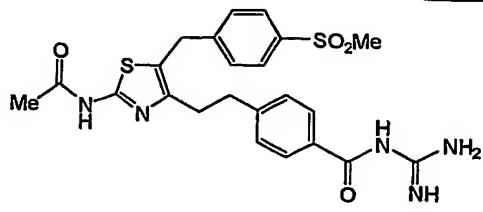
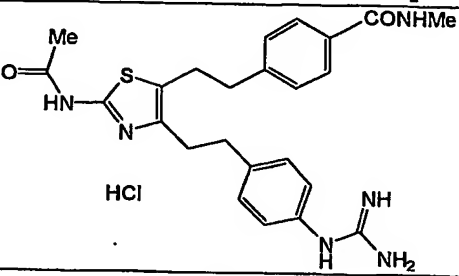
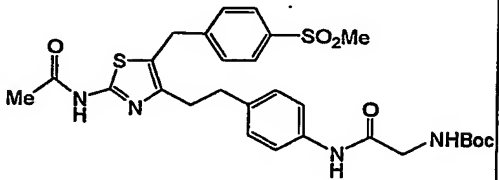
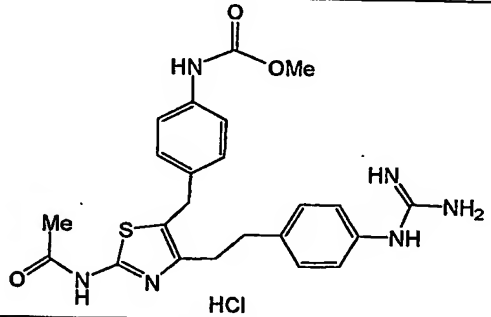
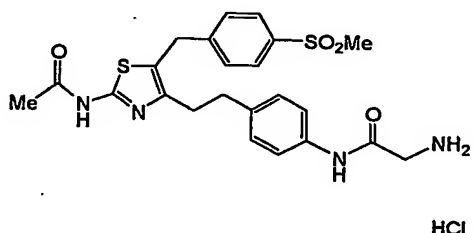
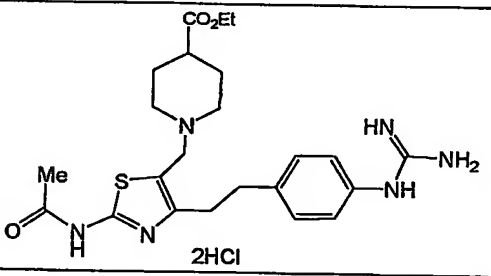
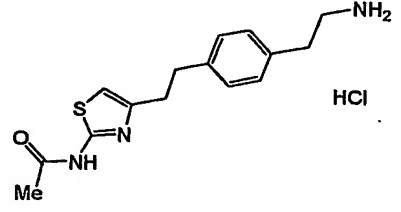
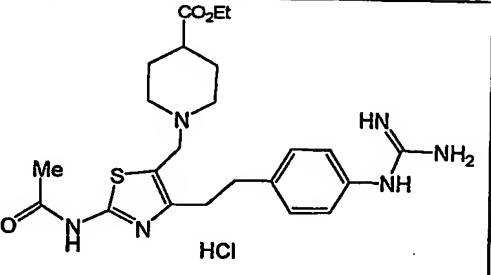
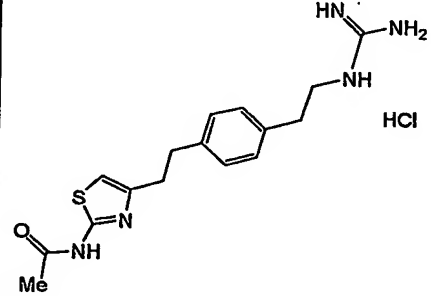
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52	 <chem>CCOC(=O)Nc1nc(Cc2ccc(S(=O)(=O)OC)cc2)c(CCN=C=N)c1CCc3ccc(NC=NN)cc3</chem>	57	 <chem>CCNC(=O)c1nc(Cc2ccc(NC=NN)cc2)c(CCN=C(N)C)c1Cc3ccc(NC=NN)cc3</chem>
53	 <chem>CCNC(=O)c1nc(Cc2ccc(S(=O)(=O)OC)cc2)c(CCN)cc1CCc3ccc(N)cc3</chem>	58	 <chem>CCNC(=O)c1nc(Cc2ccc(NC=NN)cc2)c(CCN=C=N)c1CCc3ccc(NC=NN)cc3</chem>
54	 <chem>CCNC(=O)c1nc(Cc2ccc(S(=O)(=O)OC)cc2)c(CCN=C1N=CN=C1)c1CCc2ccc(NC1=CN=CN=C1)cc2</chem>	59	 <chem>CCNC(=O)c1nc(Cc2ccc(NC=NN)cc2)c(CCN=C=N)c1CCc3ccc(NC=NN)cc3</chem>
55	 <chem>CCNC(=O)c1nc(Cc2ccc(S(=O)(=O)OC)cc2)c(CCN=C1N=CN=C1)c1CCc2ccc(NC1=CN=C1)cc2</chem>	60	 <chem>CCNC(=O)c1nc(Cc2ccc(S(=O)(=O)OC)cc2)c(CCN=C=N)c1CCc3ccc(NC=NN)cc3</chem>

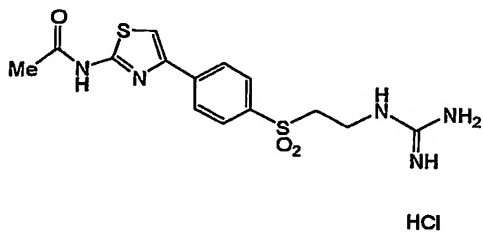
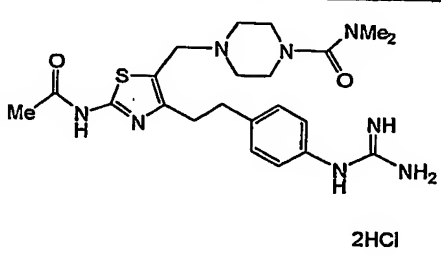
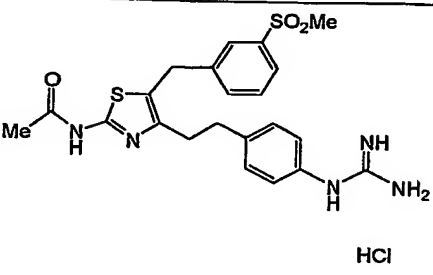
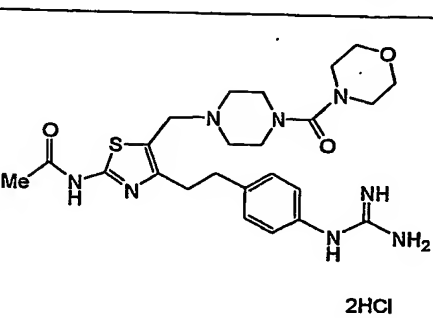
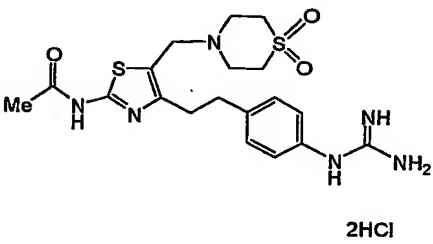
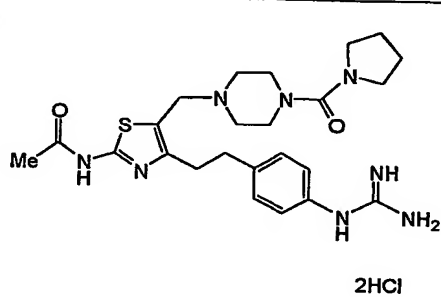
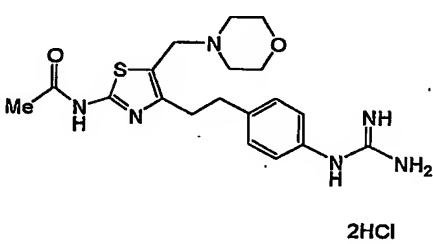
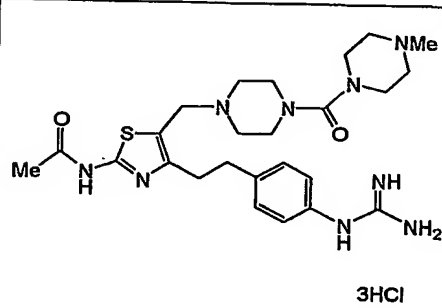
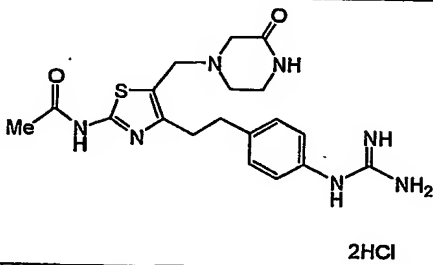
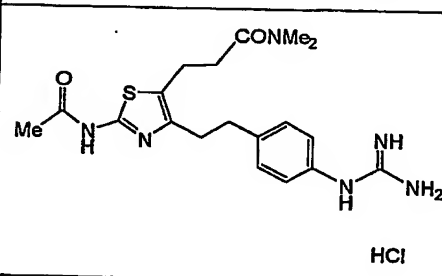
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62		67	 2HCl
63	 HCl	68	 2HCl
64	 HCl	69	 2HCl
65	 HCl	70	 2HCl

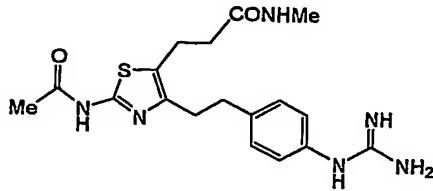
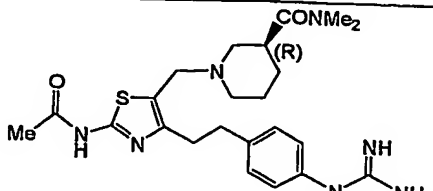
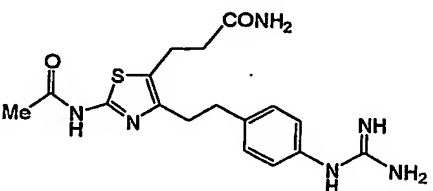
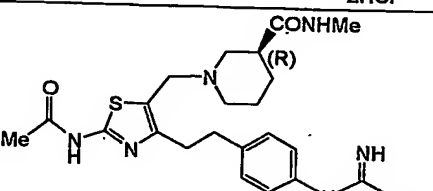
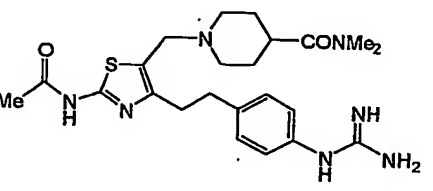
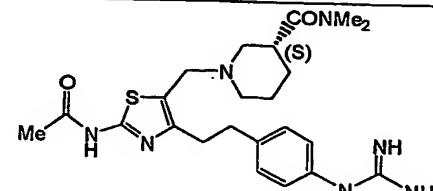
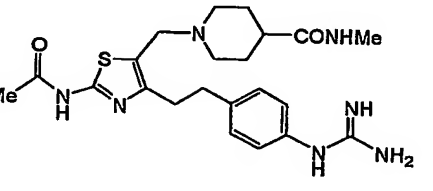
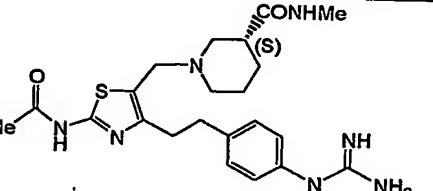
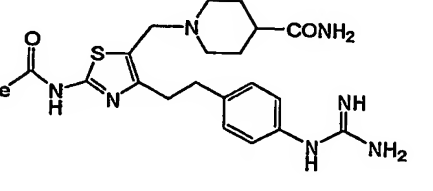
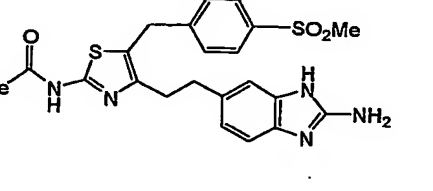
No.	Structure	No.	Structure
71	 HCl	76	 HCl
72	 HCl	77	 HCl
73	 HCl	78	 HCl
74	 HCl	79	 HCl
75	 HCl	80	 HCl

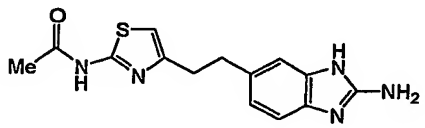
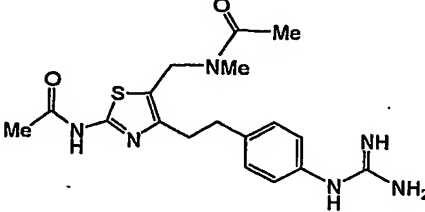
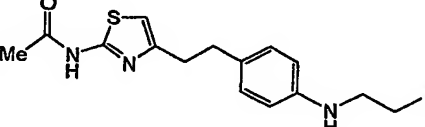
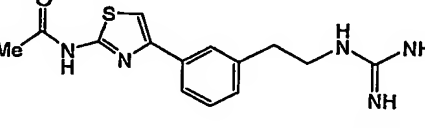
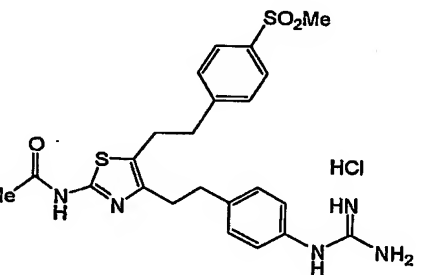
No.	Structure	No.	Structure
81	 2HCl	86	 HCl
82	 2HCl	87	 2HCl
83	 HCl	88	 HCl
84	 HCl	89	 HCl
85	 HCl	90	 HCl

No.	Structure	No.	Structure
91		96	
92		97	
93		98	
94		99	
95		100	

No.	Structure	No.	Structure
101		106	
102		107	
103		108	
104		109	
105		110	

No.	Structure	No.	Structure
111	 HCl	116	 2HCl
112	 HCl	117	 2HCl
113	 2HCl	118	 2HCl
114	 2HCl	119	 3HCl
115	 2HCl	120	 HCl

No.	Structure	No.	Structure
121	 <p>HCl</p>	126	 <p>2HCl</p>
122	 <p>HCl</p>	127	 <p>2HCl</p>
123	 <p>2HCl</p>	128	 <p>2HCl</p>
124	 <p>2HCl</p>	129	 <p>2HCl</p>
125	 <p>2HCl</p>	130	 <p>2HCl</p>

No.	Structure
131	 <chem>CC(=O)Nc1nc(Cc2ccc(cc2)Cc3cc(N)nc3)s1</chem>
132	 <chem>CC(=O)Nc1nc(Cc2ccc(cc2)Cc3cc(NC(=O)N)nc3)sc1CNC</chem> HCl
133	 <chem>CC(=O)Nc1nc(Cc2ccc(cc2)Cc3cc(NCCN)nc3)s1</chem> 2HCl
134	 <chem>CC(=O)Nc1nc(Cc2ccc(cc2)Cc3cc(NC(=O)N)nc3)sc1</chem> HCl
135	 <chem>CC(=O)Nc1nc(Cc2ccc(cc2)Cc3cc(NC(=O)N)nc3)sc1Cc4ccc(cc4)S(=O)(=O)C</chem> HCl

Example 1

Inhibitory Effect of Compound A on VAP-1 enzyme (SSAO) activity in human and rat plasma.

VAP-1 enzyme (SSAO) activity in both human and rat plasma  
5 was determined by a radiochemical-enzyme assay using  $^{14}\text{C}$ -benzylamine as artificial substrate. The enzyme suspension prepared from blood plasma was pre-incubated with Compound A in 96-well microplate at room temperature for 30 min. The enzyme suspension was then incubated with  $^{14}\text{C}$ -benzylamine  
10 ( $2 \times 10^{-5}$  mol/l final concentration) in a final volume of 50  $\mu\text{l}$  at 37°C for 1 hour. The enzyme reaction was terminated by adding 2 mol/l (50  $\mu\text{l}$ ) citric acid. The oxidized products were directly extracted into a 200  $\mu\text{l}$  toluene scintillator, and its radioactivity was measured by a scintillation spectrometer.  
15 Monoamine oxidase (MAO) and diamine oxidase (DAO, histaminase) activities were also determined by similar method using  $^{14}\text{C}$ -phenylethylamine and  $^{14}\text{C}$ -putrescine as substrate, respectively. Cloned DAO from cDNA libraries was used in human DAO assay. Inhibition activity was expressed as  $\text{IC}_{50}$  ( $\mu\text{mol/l}$ ) value.

20 Compound A completely inhibited the enzyme activity of human and rat plasma SSAO, but not the enzyme activities of other amine oxidases, such as human platelet MAO and cloned DAO, shown in Table 1.

25 Table 1. Inhibitory effect ( $\text{IC}_{50}$  values,  $\mu\text{M}$ ) of Compound A on various amine oxidase activities

Human plasma SSAO	Rat plasma SSAO	Human platelet MAO	Cloned human DAO
0.15	0.012	>100	>100

Example 2

30 Effect of Compound A on ocular permeability in diabetic rats.

Diabetes in rats was induced with an intraperitoneal

(i.p.) injection of 65 mg/ml/kg of streptozotocin (STZ) in 2 mmol/l citrate buffer (pH 4.5) after a 20-h fast. At the same time control rats were injected with an equal volume of 2 mmol/l citrate buffer. Plasma glucose level was checked by a colorimetric method. At day 3 of STZ treatment, the rats were diagnosed with diabetes showing a plasma glucose level of 350 mg/dl.

The treatment of Compound A was given daily from 2 weeks after STZ treatment for 2 weeks. At 24 hrs after final treatment of Compound A, the vascular permeability in oculus was investigated based on the leakage of dye into the vitreous 30 min after intravenous injection of fluorescein solution (40 mg/ml/kg). Permeability was expressed as vitreous/plasma ratio of fluorescein concentration measured by a fluorophotometer. At the same time, the plasma SSAO activity was checked by the radiochemical-enzyme assay using  $^{14}\text{C}$ -benzylamine ( $2 \times 10^{-5}$  mol/l final concentration) as substrate.

The significant increase of ocular permeability in diabetic rats was examined at 4 weeks after treatment of STZ and compared with that of normoglycemic normal rats. The treatment of Compound A (10 mg/kg, s.c. u.i.d.) given daily from 2 weeks after STZ treatment improved the ocular permeability, in comparison with the STZ control group (Table 2). Plasma SSAO enzyme activity also increased in diabetic rats at 4 weeks after STZ treatment, but the treatment with Compound A exhibited dose-dependent inhibition of the increased plasma SSAO activity (Table 3).

Table 2. Vitreous/Plasma Ratio of Fluorescein Concentration ( $\times 10^{-3}$ )

Normal	STZ control	Compound A treatment
$3.30 \pm 0.38^{**}$	$8.93 \pm 1.14$	$5.39 \pm 0.73^{**}$

5 Values are mean  $\pm$  S.E.M.s for 10 rats.  $^{**}p < 0.01$  vs corresponding value for STZ control by Dunnett's test.

Table 3. Plasma SSAO activity (pmol/min/ml)

Normal	STZ control	Compound A treatment
$4.40 \pm 0.34^{**}$	$10.0 \pm 0.73$	$2.51 \pm 0.26^{**}$

10

Values are mean  $\pm$  S.E.M.s for 10 rats.  $^{**}p < 0.01$  vs corresponding value for STZ control by Dunnett's test.

### Example 3

15 In the same manner as in Example 2, the effect of various VAP-1 inhibitors on ocular permeability was determined in diabetic rats.

The treatment of Compound B (0.003%, ocular instillation, u.i.d. and 0.1 mg/kg, s.c., respectively) given daily from 2  
20 weeks after STZ treatment improved the ocular permeability, in comparison with the STZ control group (Table 4).

Table 4. Vitreous/Plasma Ratio of Fluorescein Concentration ( $\times 10^{-3}$ )

Compound	Normal	STZ control	Compound treatment
Compound B 0.003%, ocular instillation	6.75 $\pm$ 0.63**	14.8 $\pm$ 0.77	9.86 $\pm$ 1.65*
Compound B 0.1 mg/kg, s.c.	9.30 $\pm$ 0.66**	15.6 $\pm$ 1.16	7.54 $\pm$ 0.80**

- 5 Values are mean  $\pm$  S.E.M.s for 10 rats. \*\*p<0.01 vs corresponding value for STZ control by Dunnett's test.

#### Example 4

Effect of eye-drop instillation with Compound A on increased  
10 retinal VAP-1 activity in STZ diabetic rats.

A 0.1% solution of Compound A was instilled into the eyes of STZ diabetic rats (10  $\mu$ l/eye) prepared in the same manner as in Example 2. To the normal group and STZ control group, a vehicle was instilled. At 6 hours from the instillation, the  
15 retina was removed from the animals and the retinal VAP-1 activity was determined.

Compound A completely inhibited the increased retinal VAP-1 activity in STZ diabetic rats, shown in Table 5.

20 Table 5. Retinal VAP-1 activity (pmol/min/mg protein)

Compound	Normal	STZ control	Compound A treatment
Compound A 0.1%, ocular instillation	5.97 $\pm$ 1.12	8.22 $\pm$ 2.60	4.86 $\pm$ 0.70

Values are mean  $\pm$  S.E.M.s for 4 rats.

Example 5

Effect of Compound A on increased retinal VEGF level in STZ diabetic rats.

STZ diabetic rats were prepared in the same manner as in  
5 Example 2. Compound A (0.1 mg/kg, sc, u.i.d.) was administered  
from 3 days to 8 weeks after the STZ administration. To the  
normal group and STZ control group, a vehicle was treated. At  
8 weeks from the STZ administration, the retina was removed  
from the animals and the retinal VEGF level was determined  
10 using a Murine VEGF ELISA kit.

Compound A completely inhibited the increased retinal VEGF  
level in STZ diabetic rats, shown in Table 6.

Table 6. Retinal VEGF level (pg/mg protein)

15

Compound	Normal	STZ control	Compound A treatment
Compound A 0.1 mg/kg, sc, u.i.d.	33.4±1.95*	42.7±3.47	28.3±2.72**

Values are mean ± S.E.M.s for 10 rats. \*p<0.05, \*\*p<0.01 vs  
corresponding value for STZ control by Dunnett's test.

20 The above result indicates that VAP-1 inhibitor is useful  
for treating a vascular hyperpermeable disease (except macular  
edema).

This application is based on application No. 60/458,370  
25 filed in the United States of America, the content of which is  
incorporated hereinto by reference.